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OBSERVATIONS ON THE HEALTH AND GROWTH OF CHILDREN IN AN INSTITUTION *

L. EMMETT HOLT, M.D., AND HELEN L. FALES

NEW YORK

Through the courtesy of the trustees of a semicharitable institution for children of both sexes, we have had the opportunity to make observations for thirty-one months on the growth and nutrition of the children who were inmates. The data obtained have furnished some very interesting statistics on the growth and general condition of children living under institutional conditions.

THE INSTITUTION

The institution was a Roman Catholic home and school for poor children, conducted by Sisters of a French order. During the first twenty months of our study, it was housed in an old-fashioned building occupying a plot about 100 feet square in the heart of the uptown business section of New York, which had been its home for over fifty years. This building was surrounded by tall office buildings, which cut off from it much light and fresh air. It was, therefore, dark and rather gloomy, though scrupulously clean. The refectories and kitchen were in the basement, requiring artificial light. The schoolrooms and dormitories were on the upper floors and had light on at least one side. The children were divided according to age into three groups for each sex. They slept in dormitories accommodating from twenty to thirty children each. Each child had a separate cot. The bathing facilities consisted of shower baths and wash bowls. The playgrounds, one for the boys and one for the girls, consisted of two small yards in the rear of the building, enclosed by high brick walls, the size of each being about 30 by 40 feet.

A summer home in the country was maintained where each child spent one month, some of the children going in July and the rest in August. A few who were in special need of the vacation were allowed to remain through the two months.

In January, 1922, the institution was moved to a country estate about 30 miles from New York. The new home consists of several buildings

* Received for publication, April 19, 1923.

* From the laboratories of the Rockefeller Institute for Medical Research and the Babies' Hospital.

providing ample space and plenty of light and air. There are playrooms in the dormitory building and in the schoolhouse. There are two large outdoor playgrounds, one for each sex, equipped with swings, slides, etc.

INMATES

Most of the children of this institution are not of the poorest classes, since as a rule a moderate fee is charged for their care. A few of the children were orphans; many were half-orphans, and some had both parents. The nationalities were chiefly French, Spanish, Italian and Irish. On the first examination and at subsequent observations, the children were with but few exceptions in excellent physical condition. They were happy and gay, not suffering in the least from institutional repression, although they were living under strict regulations. The schoolwork is the same as that of the public school. No systematic physical education is given, although the girls and small boys have lessons in folk dancing and dramatics.

The ages of the boys ranged from 4 to 14, the girls from 4 to 16. Many of the children remain in the institution for the entire period covered by the age limit. Some remain only a few months. There was, consequently, considerable change, from time to time, in the material on which our study was based.

GENERAL HEALTH

The general health of the children is supervised by a visiting physician. He gives each applicant for admission a complete examination, and excludes defective children and those acutely ill or suffering from contagious diseases. Malnutrition is not a cause for exclusion, but is rather made a reason for admission. The rule of the institution is to quarantine for at least two weeks each child admitted. Minor ailments are treated by one of the sisters, who acts as nurse and administers cathartics when necessary. About once in two weeks each child in the institution is given a dose of cascara sagrada as a precautionary measure. In the spring all children receive a tonic for a few weeks. Common colds are dealt with promptly by administration of a hot drink and an active cathartic.

The effectiveness of the general routine which is followed in the institution is manifest in the always excellent physical condition and the good digestion of the children. As an example, the cleanness of the tongues of the children was especially noteworthy. On one examination day special observations were made of the condition of the mouths. Of 144 children, only twenty showed even the slightest coating of the tongue, and only five showed marked coating, these being mostly older girls who were working in the kitchen.

During our study there was surprisingly little illness of any kind in the institution; no epidemics of any sort occurred, and almost no cases of serious illness. There were no deaths in the institution during the period of observation. One child was removed to a hospital suffering from appendicitis, from which he died. The infrequency of any important illness is further shown by the fact that in all the twenty-two weighing days, on each of which an average of 135 children were examined, there were only seventeen absences on account of illness.

When the institution was in New York many of the children had decayed teeth, fully 30 per cent. showing this condition at first examination. Since the removal to the country, much of this has been corrected. Adenoids and hypertrophied tonsils were found in about the usual frequency—nearly 30 per cent. of the children. During our period of study forty of the children had tonsillectomies. The children as a rule had excellent color, especially after removal to the country.

In general, it may be said that the surprisingly good physical condition of these children reflects great credit on the management of the institution. The impression is prevalent that children living in institutions decline in general health and vitality, and that their growth and physical development are inhibited. Our observations of these children show that this is not a necessary result, and that the contrary may be true. The carefully controlled life in a properly managed institution, the regular hours, the good food and the lessened chances of infection, because the children do not come in contact with other children as do those who attend public school, make it possible to keep these children in excellent health, in fact, in much better condition than children in most private homes.

ROUTINE

The children rise at 6 a. m., and wash and dress in silence. At 7 they have breakfast, which, like all meals is taken without talking. This practice has been followed because it was found that the children ate better than when talk and play were permitted. Like most children, they eat rapidly, seldom taking over twenty minutes for a meal, even a dinner of three courses. From 9 a. m. until 12 m., they are in school. At 12 m., dinner is served, and school follows from 1 to 3 p. m. From then until supper is play time. The older girls spend a portion of this time in sewing. The younger children have supper at 5 p. m. and go to bed at 6. The older children have supper at 7 p. m. and go to bed at 8. The older girls help in the general housework, and in the country the older boys assist about the grounds.

While in the city, the only outdoor exercise, except the time spent in the playyards, was a trip to Central Park on Sunday morning. The children walked to and from the park—about 1 mile—and played there for about one hour. In the country the children do considerable

walking about the grounds, since the school is some distance from the other buildings. They play out doors each afternoon, the weather permitting.

From a hygienic point of view the conditions in the country are a great improvement over those in New York, but, as will be shown later, this change in environment apparently has had little effect either on health, weight gain, or general appearance of the children, possibly because the physical condition was so good while they were living in the city.

DIET

Until about one month before our observations were begun the regular diet included little milk, although in other respects it was excellent. Tea and cocoa containing a very little milk had been given. Some additional milk had been used in the preparation of other food. A large amount of meat had been provided, it being served once and sometimes twice a day, and meat soup was served twice a day. A month before our observations were begun the addition to the diet of a pint of milk daily for each child had been made. The amount of meat served was somewhat reduced and no meat or meat soup was served at supper.

TABLE 1.—*Menu for a Week*

	Breakfast	Dinner	Supper
MONDAY	Bread and butter Cocoa	Meat soup Mutton stew Bread and cake	Milk soup Bread and jelly Fruit
TUESDAY	Oatmeal Bread and jelly Cocoa	Meat soup Roast beef, cabbage Bread, bananas	Baked beans Bread and butter Milk
WEDNESDAY	Cornflakes Milk and bread	Soup with carrots, onion Veal, tomato stew Bread and cake	Rice pudding Bread and jelly Milk
THURSDAY	Hominy Milk Bread and jelly	Meat soup Boiled beef Potatoes Bread and apples	Tapioca pudding Bread and butter Cocoa
FRIDAY	Oatmeal Bread Cocoa	Julienne soup Fish or egg Bread and bananas	Milk soup Baked beans Bread and jelly
SATURDAY	Bread and butter Cocoa	Meat soup Mutton Lettuce Bread and prunes	Bread pudding Apple sauce Bread and milk

Table 1 gives a typical weekly diet after these changes had been made. This dietary, with only minor variations, has been used throughout the period of our study.

The cocoa served at breakfast was made with milk without adding water. At supper the children either drank milk plain or took it in the form of milk soup, that is, hot milk with some seasoning and with bread added. Little butter was used. Soups were made from meat stock with the addition of vegetables, and were served with large pieces of stale

bread added. The dessert was usually fresh fruit or small sweetened rolls or cakes, which were often donated by hotels or restaurants. The children have always received throughout the year a fair amount of green vegetables; since the removal to the country, this has been somewhat increased. All the children received the same food, the quantity only being varied according to the age. Bread was allowed *ad libitum*, and the amounts consumed were astonishing. Each child usually ate at least two large pieces at each meal and many, especially the larger boys, took four or five slices. In addition to the amount taken at meals, a large piece was usually served to each child in the afternoon.

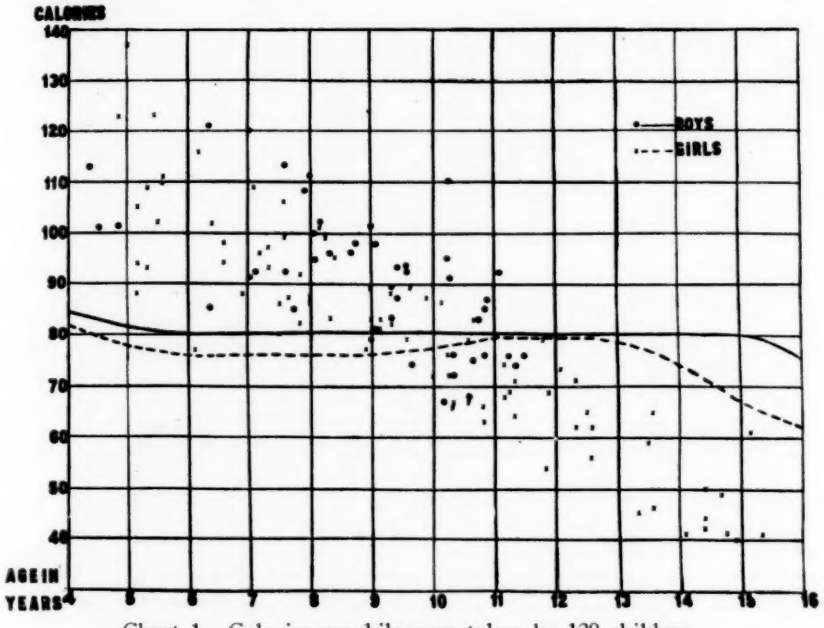

Chart 1.—Calories per kilogram taken by 129 children.

In October, 1920, the approximate amount of food taken for two consecutive days by each child then in the institution was ascertained. From the data obtained the caloric intake of each child, the percentage of distribution of the calories and the amount of fat, protein and carbohydrate were calculated. As a whole, the total caloric intake was high, except in the case of some of the older girls. It is suspected, however, that the amounts recorded for this group did not represent their total food intake, since they were working in the kitchen and refectories and had ample opportunity to obtain additional food.

The average distribution of the calories taken was: fat, 22 per cent.; carbohydrate, 61 per cent., and protein, 17 per cent. This distribution is somewhat different from what we have considered ideal: viz., fat, 35

per cent.; carbohydrates, 50 per cent., and protein, 15 per cent. The fat furnished too low a proportion of the total calories, and the carbohydrate too high a proportion. The supply of vitamin A was therefore probably not up to the average. The carbohydrate intake was very high. This was mainly due to the large amounts of bread consumed. The protein intake was higher than the average. The protein intake per kilogram was liberal. About 56 per cent. was animal protein and 44 per cent. vegetable protein, a somewhat lower proportion of animal protein than the optimum. However, the generous total protein intake undoubtedly compensated for this. The supply of mineral

TABLE 2.—*Typical Diet Sheet of a Medium Sized Boy* (Average Amount of Food Taken for Two Days)*

Article of Food	Amount	Calories			
		Fat	Carbohydrate	Protein†	Total
Milk	16 oz.	149	94	69	312
Butter	1½ tsp.	56	0	0	56
Cocoa	1 tsp.	7	4	2	13
Cake	0.5 piece	15	54	8	77
Gravy	2 oz.	11	3	2	16
Jelly	¼ oz.	0	25	0	25
Sugar	2 tsp.	0	49	0	49
Apple	50 gm.	2	22	1	25
Vegetables, mixed	1 tbsp.	1	5	1	7
Cabbage	4 oz.	1	2	4	7
Tomato	3 oz.	2	18	4	24
Meat	3 oz.	99	0	90	189
Soup	10 oz.	11	14	54	79
Rice pudding	4 oz.	62	141	35	238
Tapioca pudding	4 oz.	76	121	31	228
Bread‡	12 pieces	43	783	135	961
Total food		535	1,335	436	2,306
Calories per kilogram		23	57	18	98
Calories per pound		10	28	9	44
Distribution of calories		23	58	19	
Grams daily		58	326	106	
Grams per kilogram		2.4	13.8	4.5	
Grams per pound		1.1	6.3	2.0	

* W. A., aged 8 years and 9 months, weight, 52 pounds (23.6 kg.), height, 47 inches (117.5 cm.); average weight for height; undersize for age.
† Proportion of animal protein, 56 per cent.; of vegetable protein, 44 per cent.
‡ Amount includes that added to soup, tomato, etc.

salts, especially calcium, was possibly low, since only 1 pint of milk was given.

Chart 1 shows the calories per kilogram taken by forty-six boys and eighty-three girls. The line shown on the chart is that previously estimated by us as a desirable average.[1]

It will be seen that the children up to the age of 10 years took considerably more than the theoretical requirement, while those over 10 often received less. This was largely due to the manner of serving the meals to the children. The food for the entire dining room was brought to the table in large containers, and a sister served it to the

1. Holt, L. E., and Fales, H. L.: Food Requirements of Children; Total Caloric Requirements, Am. J. Dis. Child. **21**:1 (Jan.) 1921.

children, making some variation in amount according to the size of the child. By this practice, however, the smaller children received *proportionally* more than the larger ones. For example, a girl weighing 40 pounds (18 kg.) would receive at least half as much food as a girl weighing over 100 pounds (45.4 kg.). Of such items as fruit, cakes, etc., as well as milk, practically the same quantity was given to all the children, regardless of size. Therefore, since the amount of food taken was governed not by the desires of the children but by the judgment of the sister who served, the values are not to be taken as a guide for the *normal* caloric requirement. It is interesting, however, to note that the young children took eagerly so much food, and with apparently no ill effects.

Table 2 gives the form in which the diet of each individual was studied.

TABLE 3.—*Number of Observations*

Number of Observations	Boys	Girls	Total
18 - 22	21	41	62
12 - 17	18	18	36
7 - 11	37	54	91
4 - 6	17	18	35
1 - 3	58	64	122
Total	151	195	346

TABLE 4.—*Duration of Observation*

Duration	Boys	Girls	Total
2 yrs. - 2 yrs. 7 mos.	21	48	59
1½ - 2 yrs.	14	7	21
1 yr. - 1½ yrs.	23	41	64
6 mos. - 1 yr.	29	30	59
3 - 5 mos.	12	15	27
Under 3 mos.	30	43	73

OBSERVATIONS ON GROWTH

During the thirty-one months of our study, the children were weighed at frequent intervals, usually once a month, and the height was measured about once in three months. In all, 2,995 observations on weight were made on 346 children, 151 boys and 195 girls. The number of observations of each child varied according to the length of stay in the institution. Table 3 gives an idea of the number of observations for each child, and Table 4 the approximate duration of the period of observation of each child.

The height was measured without shoes. The weights were taken without shoes, and in the usual indoor clothing. Heavy jackets or sweaters were removed. The children did not wear an institutional uniform, but there was much more uniformity in clothing than would be found in a public school group. The clothing was simple, not excessive in weight, and varied very little for children of the same age and size.

Various weighings were made of the average clothing worn in the winter and summer, not including shoes, coats and sweaters. This weight of the clothing was practically the same for boys and girls. It was found that for the large children, that is, those over 60 pounds (27.2 kg.) in weight and over 50 inches (125 cm.) in height, the average weight of winter clothing was 2 pounds; that of the summer clothing, 1.5 pounds. For the smaller children, weighing from 40 to 60 pounds (18 to 27.2 kg.) and ranging from 35 to 50 inches (88 to 125 cm.) in height, the average was 1.5 pounds for winter clothing and 1 pound for summer clothing. The weights taken have all been reduced to net weight by making the deduction for clothing just mentioned. The purpose of this was to secure a more accurate comparison of the weights taken at different seasons. This correction for clothing is, of course, not absolutely accurate for children of all ages. However, since the same reduction to net weight was made in the successive weighings of each child, the gain or loss in weight is exact.

TABLE 5.—*Distribution of Children According to Nationality*

Nationality	Number of Boys	Number of Girls	Total
American	9	14	23
French	27	30	57
Italian	37	47	84
Spanish	30	32	62
Irish	23	39	62
Balkan	6	10	16
Central European	19	23	42
Total	151	195	346

The data obtained at the initial examination of each child have been analyzed to determine the relation of the weight to height, weight to age and height to age, and the variation of each of these relations according to nationality.

The racial distribution is shown in Table 5. The Central European group includes mostly Germans, a few Russians, Austrians, Scandinavians, Bohemians, one Hungarian and one Pole. The American group includes children born in this country and whose parents were also born here, but whose parentage was so mixed as to eliminate racial differences. Many of the children classed in the national groups were born in this country, but the parents were not; or the racial influence was so obvious that the classification was evident.

Relation of Weight to Height.—This relation on the first examination is shown in Charts 2 and 3. The solid line shows the standard weight for height and is based on the values given by Holt and Howland.[2] These values are derived from the figures obtained by ten dif-

2. Holt, L. E. and Howland, J.: Diseases of Infancy and Childhood, Ed. 8, New York, D. Appleton & Co., p. 23.

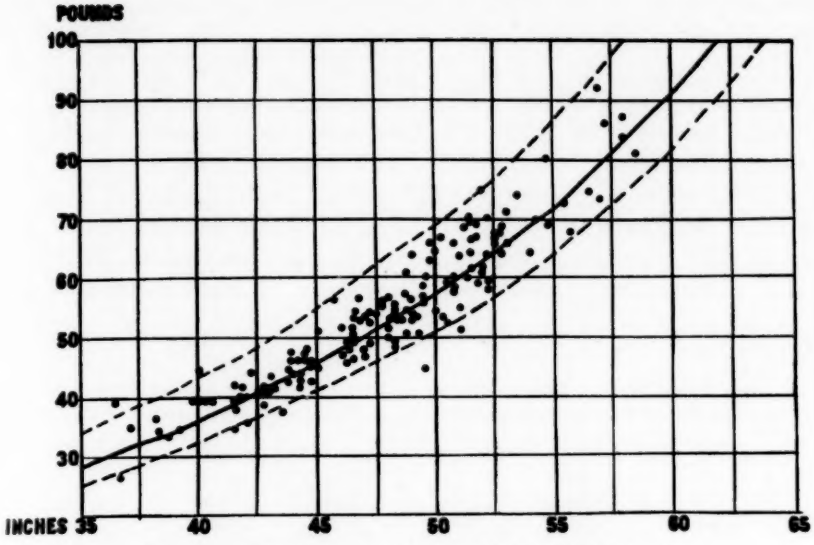

Chart 2.—Relation of weight and height (151 boys).

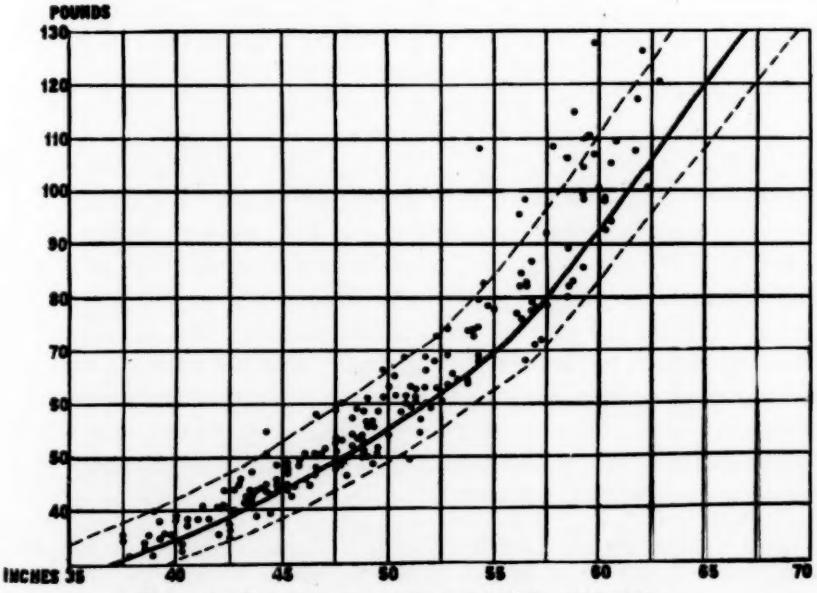

Chart 3.—Relation of weight and height (195 girls).

ferent authors and are based on more than 100,000 observations. The dotted lines in each chart mark the zone including the weights of boys and girls, respectively, 10 per cent. below and 20 per cent. above the standard weight for height. The charts show that the children of the institution were with very few exceptions near average weight for height, the tendency being slightly above the average.

A doubt has been expressed by some writers as to the propriety of using a single weight-for-height standard for different races. It was found that nationality had no apparent effect on the weight-height ratio of the children studied in the institution. Table 6 shows the exact relation of the height to weight and the influence of nationality on that ratio.

The adoption of a definite limit for the percentage below average weight as an evidence of malnutrition has frequently been questioned. It has been argued that, if this is done, some perfectly healthy children

TABLE 6.—*Relation of Weight to Height in Different Nationalities*

Nationality	Normal Weight for Height (10% Below to 20% Above Average)		Under Weight for Height (More than 10% Below Average)		Overweight for Height (More than 20% Above Average)		Total Number of Children
	Number	Percentage of Total	Number	Percentage of Total	Number	Percentage of Total	
American	23	100	0	0	0	0	23
French	50	88	3	5	4	7	57
Italian	82	98	0	0	2	2	84
Spanish	56	90	2	4	4	6	62
Irish	58	94	0	0	4	6	62
Balkan	15	94	0	0	1	6	16
Central European	39	93	2	5	1	2	42
Total	323	93	7	2	16	5	346

might be classed with those clearly not normal, especially if any definite variation according to race does exist. The most commonly accepted limits used in classifying children as normal in weight for height are from 10 per cent. below the average to 20 per cent. above. It is interesting to apply this standard to the group of children studied by us. There were only six boys and one girl who were more than 10 per cent. below average weight for height. Since there were so few underweight children, the details regarding them may be of interest. It will be noted that only one of these children had been in the institution more than one month when examined.

CASE 1.—Boy, French, aged 7 years and 4 months, examined six days after admission, and nutrition graded as II, had no physical defects. He remained in the institution only twelve days.

CASE 2.—Boy, French, aged 7 years and 4 months, examined fourteen days after admission, and nutrition graded III, suffered from rachitis of long standing, enlarged glands, bad teeth and scaly skin. Only one observation was made.

CASE 3.—Boy, Spanish, aged 4 years and 9 months, examined two weeks after admission, was mentally defective. He gained 3 pounds in the twelve months following the first examination.

CASE 4.—Boy, Spanish, aged 7 years and 7 months, examined one month after admission, and nutrition graded II, was highly nervous, with enlarged adenoids and tonsils (no operation was performed). He gained 5½ pounds in the next six months.

CASE 5.—Boy, German, aged 5 years and 3 months, examined two weeks after admission, and nutrition graded II, was one of twins (see Case 6). He had rickets of long standing, bad teeth and frequent minor illnesses. Inheritance was bad. He gained 5 pounds in weight and three-fourth inch in height in fourteen months.

CASE 6.—Boy, German, aged 5 years and 3 months, one of twins (Case 5), presented the same clinical picture as did his brother. He weighed a little more than the brother on admission, but made less progress. He gained 2 pounds in weight and 1.75 inches in height in fourteen months.

CASE 7.—Girl, French, aged 8 years and 6 months, examined two months after admission, and nutrition graded II, had bad teeth. She gained 1 pound in three months.

This proportion of underweight children is much smaller than that reported in most groups of schoolchildren. Whether the ample food and the excellent hygiene of the institution account for this is an interesting question. All but seventy-two of the children when first examined had been resident for at least one month and all but four for at least two weeks. It is probable that any previously existing underweight may have been corrected by the excellent food and hygiene even in as short a time as one month. It is the usual experience that children who are much below weight make a rapid initial improvement when they are given a proper diet and are placed in better environment. In selecting children for admission, preference was given by the admitting physician to those obviously in need of improved living conditions. In consequence, it is fair to assume that there had been some improvement in weight during the first few weeks of residence.

Sixteen children were considerably overweight; that is, they were more than 20 per cent. above the average weight for their height at first examination. Nine of these sixteen overweight children were girls between 11 and 15 years of age, years in which a marked degree of plumpness is frequent. Of the sixteen children, four gained more than the average in the succeeding months; five gained at the average rate; two gained less than average, and one lost weight. Four did not remain in the institution long enough for subsequent observation. It is evident, however, that the condition of overweight had no definite relation to their further progress in growth.

Relation of Height to Age.—Wide variation of height in relation to age is seen in healthy children of all races. While the relation of height to exact age has little significance in individuals, it is interesting when

groups are considered. Charts 4 and 5 show the relation of height to age. The children as a group, especially the girls, were short, as compared to the averages established from statistics obtained by the examination of mixed groups of American schoolchildren. Of 149 boys, sixty-four (43 per cent.) were about average height for age, or more than average height, and eighty-five (57 per cent.) were not up to the average height for age. Of 195 girls, sixty-five (33 per cent.) were about average height for age, while 130 (67 per cent.) were under average height for age.

Table 7 gives the distribution of these values according to nationality. The Spanish children were the nearest to the average in height-age relation. The Italian children were shortest. The Irish as a group were also short. It was of interest in studying the height to consider separately the children who had been resident in the institution for a long period before our observations were begun, since the diet previously

TABLE 7.—*Relation of Height to Age in Different Nationalities*

Nationality	Above or About Average Height for Age		Under Average Height for Age		Total Number of Children
	Number	Percentage of Total	Number	Percentage of Total	
American	11	48	12	52	23
French	23	40	34	60	57
Italian	22	26	62	74	84
Spanish	33	53	29	47	62
Irish	20	33	41	67	61
Balkan	3	19	13	81	16
Central European	17	41	24	59	41
Total	129	37	215	63	344

had been notably deficient in calcium because of the small amount of milk given. Since the calcium supply is of undoubted importance in growth in height, it is not surprising that these children were short. Of eighty-nine children who had been resident in the institution for more than one year previous to our investigation, only eighteen (20 per cent.) were of average height for age, while seventy-one (80 per cent.) were under average height. Of these children, twenty-eight were as much as 4 inches (10 cm.) (almost two years' growth) under the average height for age, while ten were over 6 inches (15 cm.) under average height.

Relation of Weight to Age.—The relation of weight to age showed, as would be expected, very wide variation, but on the average the children were near the usual weight for age. This was due to the fact that, although short, most of these children were of more than average weight for height.

Progress.—Most of the children who were under observation for a long enough period to allow any conclusions in regard to their progress

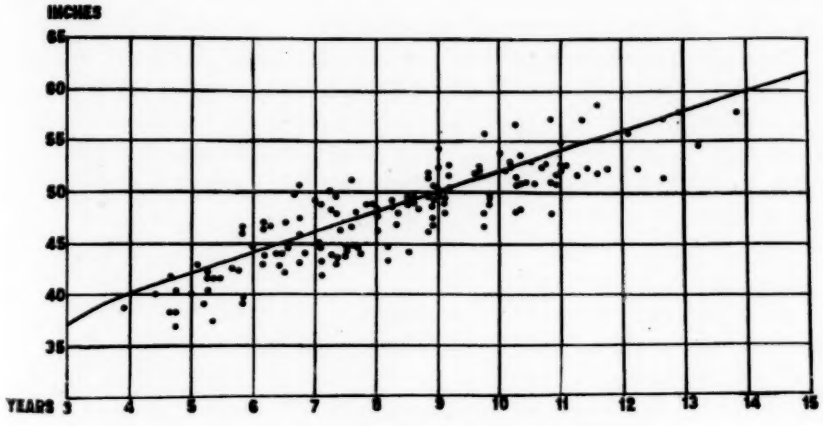

Chart 4.—Relation of height and age (149 boys).

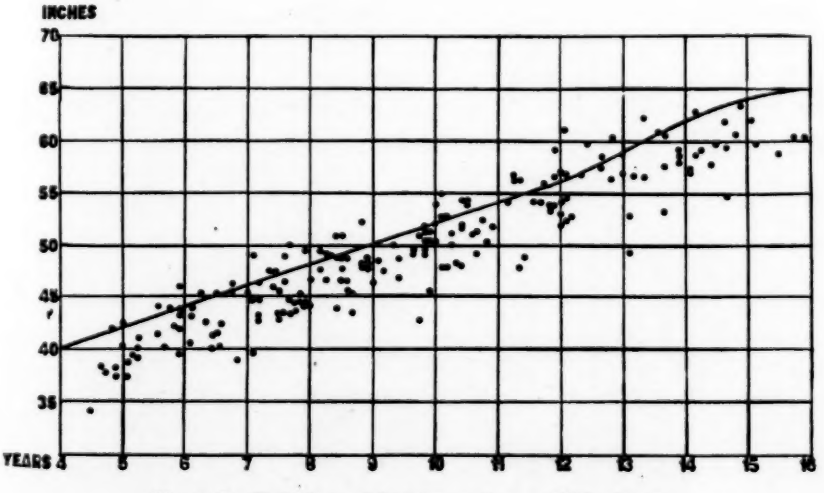

Chart 5.—Relation of height and age (195 girls).

in growth gained well and steadily in both weight and height. A critical survey of the rate of growth, however, showed that many of these children failed to make normal progress.

Table 8 shows the rate of growth of 148 children who were under observation for one year or more. The greater number of the boys gained weight normally. Two thirds of them made also a normal gain in height. A little more than half the girls gained weight normally, and only one half made an average gain in height. When it is recalled that many of the children, especially the girls, were overweight or of average weight for age, these figures for rate of gain in weight are what might have been expected.

The progress in height is, however, a different matter. Most of these children were under average height for age, and it might have been expected, therefore, that in their good environment and with their liberal food allowance the height gain would proceed at more than average rate. There may be several reasons why this did not occur.

TABLE 8.—*Progress in Weight and Height*

		Weight				Height			
		Progress Normal or Better than Normal		Progress Less than Normal		Progress Normal or Better than Normal		Progress Less than Normal	
	Total Number	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Boys.....	55	44	80	11	20	36	65	19	35
Girls.....	93	54	58	39	42	48	51	45	49
All.....	148	98	66	50	34	84	57	64	43

It is possible that the diet, which included only 1 pint of milk daily, was not adequate in mineral salts, especially in calcium. The observations of some recent writers, notably Sherman,[3] indicate that since the other articles of food contain but little calcium, 1 quart of milk daily is needed by the growing child to supply a sufficient amount. Again, it is one of the observed facts in regard to growth that short children grow more slowly and tall children more rapidly than the average; so that, as a rule, short children become short adults, and tall children, tall adults. Many of these children belonged to short races, the Italian and French; but the short stature and slow growth were found in the case of the Irish, who are not racially short. Whether it is possible to stimulate an established slow rate of growth by special diet is an interesting question. It has been proved possible within certain limits to do this with animals whose growth has been retarded by insufficient mineral salts, provided the retardation has not persisted too long.

3. Sherman, H. C., and Howley, E.: J. Biol. Chem. **53**:375 (Aug.) 1922; J. Home Econ. **14**:413 (Sept.) 1922.

Table 9 shows the average six months' increment in weight and height, according to age, of the children studied. For comparison, there is given the average six months' increment (Holt and Howland, p. 22), which has been derived from large numbers of observations. The standard values for six months are not absolutely exact, since they have been obtained by dividing the usual yearly increment by 2, to obtain a value for a six months' period. The difference is unimportant. It is evident that the six months' growth of these children was, on the average, very near the normal. The fact that the average height gain was so near the normal is especially interesting in view of

TABLE 9.—*Average Yearly Increment in Weight and Height*

	Boys					Girls				
		Weight Gain (Pounds)		Height Gain (Inches)			Weight Gain (Pounds)		Height Gain (Inches)	
Year of Age	Number of Cases	Average	Normal*	Average	Normal*	Number of Cases	Average	Normal*	Average	Normal*
4 - 4.5	1	1.0	2.0	1.25	1.25	0	...	2.0	....	1.25
4.5 - 5	1	3.0	2.0	1.25	1.25	1	3.0	2.0	0	1.25
5 - 5.5	3	1.5	2.0	1.25	1.00	6	1.3	2.0	1.0	1.00
5.5 - 6	6	2.1	2.0	1.00	1.00	9	1.9	2.0	1.1	1.00
6 - 6.5	4	3.1	2.0	1.10	1.00	11	1.9	2.0	1.0	1.00
6.5 - 7	7	2.9	2.0	1.10	1.00	15	1.9	2.0	0.75	1.00
7 - 7.5	8	2.0	2.4	1.00	1.00	14	2.6	2.25	1.00	1.00
7.5 - 8	11	3.0	2.4	1.00	1.00	18	2.1	2.25	0.95	1.00
8 - 8.5	11	2.8	2.6	0.75	1.00	21	2.0	2.5	0.90	0.80
8.5 - 9	13	2.9	2.6	1.00	1.00	20	2.9	2.5	1.0	0.90
9 - 9.5	20	2.2	3.0	1.00	1.00	21	1.6	2.6	0.95	1.10
9.5 - 10	14	2.9	3.0	1.00	1.00	13	2.8	2.6	1.1	1.10
10 - 10.5	13	2.4	2.5	0.90	0.8	19	3.4	3.2	1.0	1.00
10.5 - 11	16	3.4	2.5	1.00	0.9	18	2.2	3.3	1.0	1.00
11 - 11.5	11	3.8	3.2	1.10	0.9	12	4.8	4.7	1.2	1.25
11.5 - 12	6	3.9	3.3	1.00	0.9	9	2.3	4.8	1.15	1.25
12 - 12.5	4	6.0	4.0	1.35	1.0	8	5.4	5.25	1.15	1.00
12.5 - 13	..	...	...	....	....	9	6.5	5.25	0.90	1.00
13 - 13.5	..	...	...	....	....	8	2.5	4.8	0.95	1.00
13.5 - 14	..	...	...	....	....	6	7.1	4.7	1.0	1.00
14 - 14.5	..	...	...	....	....	7	3.0	3.8	0.95	0.60
14.5 - 15	..	...	...	....	....	9	5.3	3.7	0.63	0.60
15 - 15.5	..	...	...	....	....	5	3.3	3.0	0.45	0.40
15.5 - 16	..	...	...	....	....	1	2.5	3.0	0.50	0.30

* Holt and Howland: Diseases of Infancy and Childhood, p. 22.

the observation previously made that many of the children gained in height at less than the average rate. It is evident that the others gained at enough more than the usual rate to compensate for those whose gain was less, thereby making the average very close to the values usually found.

Seasonal Growth.—A good deal of interest has been shown recently with regard to the variation in growth in different seasons of the year. The figures published by Porter [4] indicate that there are such variations, and that these are quite regular; viz., that the increase in weight during the six months from June to December far exceeds that in the six

4. Porter, W. T.: Am. J. Physiol. **52**:121 (May) 1920.

months from December to June. Gebhart[5] has recently published figures showing exactly what percentage of the annual gain in weight may be allocated to each of the calendar months. In his theoretical schedule, 60 per cent. of the gain for the entire year is made in the four months August to November, inclusive. The observations analyzed by him were quite numerous, but since his conclusions were based, partly upon the growth of one group of children who were followed for only four consecutive months and partly upon the growth of other groups who were followed but eight months, they seem hardly warranted by his facts.

Seasonal variations in growth have been ascribed to changes in environment, in activity and in diet, and to minor illnesses. It was thought that observations on the children studied by us might furnish some interesting data on this point, because their life was so nearly the same for the entire year. Their diet was known both qualitatively and quantitatively, and seasonal changes in diet were slight. Except for a single month in summer, their activity varied but little during the different periods of the year. Their environment remained the same. Besides, as a group they were remarkably free from serious or even minor illnesses.

We have analyzed the weight records with reference to the following points: (1) a comparison of the winter and spring period (December to June) with the summer and autumn period (June to December); (2) the average gains made in each calendar month by boys and girls, and (3) the average gains for each successive month of the children who were followed for long periods. The average gain of the girls in 187 summer periods was 3.26 pounds; and in 144 winter periods, 3.34 pounds. The average gain of the boys in 113 summer periods was 3.50 pounds, and in eighty-five winter periods, 2.44 pounds. In the girls, there was therefore little difference between the summer and winter periods, the winter period showing, however, a slight increase. In the boys, the average summer gain was greater by one pound.

In graphic Chart 6 are shown the average gains by calendar months for boys and girls. Not all of the children were observed throughout the entire period, some being studied for two and a half years, some for only one year and some for only a few months. There were not less than forty-three and not more than fifty-five boys weighed each time, and not less than sixty-eight and not more than ninety girls. In 1920, there was a period of four months, June to September; in 1921, one of three months, July to September, and in 1922, one of two months, August and September, in which monthly weighing could

5. Gebhart: Height and Weight as an Index of Nutrition, Bull. New York Ass'n for Improving Condition of the Poor, 1922.

not be made. The total weight gain for these periods has, therefore, been divided equally into monthly increments. Accordingly, the values for these months, as shown on the charts, are somewhat arbitrary.

There was much less variation shown in the gains of the girls than in those of the boys. The loss in weight in May and June, 1922, for the boys, and in June and July of the same year for the girls may be, in part, explained by more than usual activity, since this was their first warm season in the country, removal from the city having occurred in

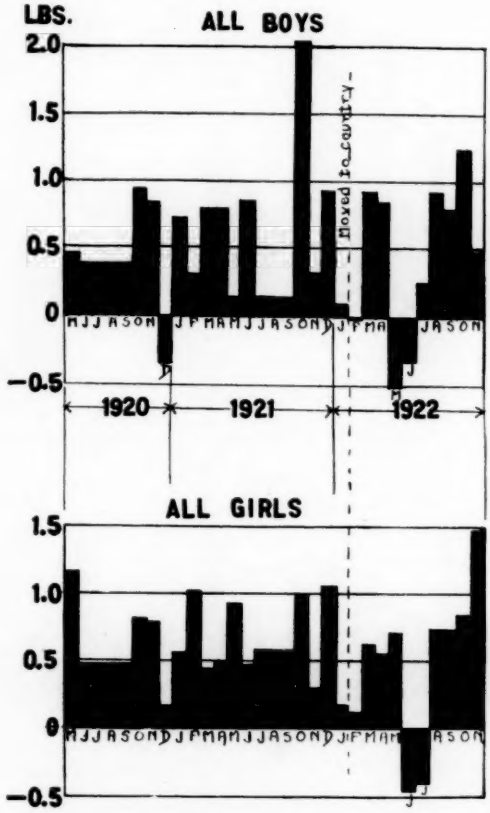
LBS.
ALL BOYS
2.0
1.5
1.0
0.5
0
−0.5
Moved to country
M J J A S O N D J F M A M J J A S O N D J F M A J A S O N
1920
1921
1922
ALL GIRLS
1.5
1.0
0.5
0
−0.5
M J J A S O N D J F M A M J J A S O N D J F M A M J A S O N

Chart 6.—Average gain in weight by months.

the previous January. This explanation is not entirely satisfactory, as the girls made good gains in May, the month in which the greatest loss for the boys is recorded.

About the only conclusion that can be drawn from these charts is that monthly gains are not at all regular even in healthy children with the same food, the same habits, and the same environment, and that periods of two or three months of little gain are likely to be followed by a period of great gain, as is strikingly shown by the boys in 1921.

The difference in gain during the same calendar months of successive years is also striking. June, November and December, especially, show wide variations in different years for both sexes.

The great variation in monthly gains is even better brought out in Chart 7, where are shown the average gains for the children who were observed continuously during practically the entire period of our study. Although this is not a large group, the results are very striking. In

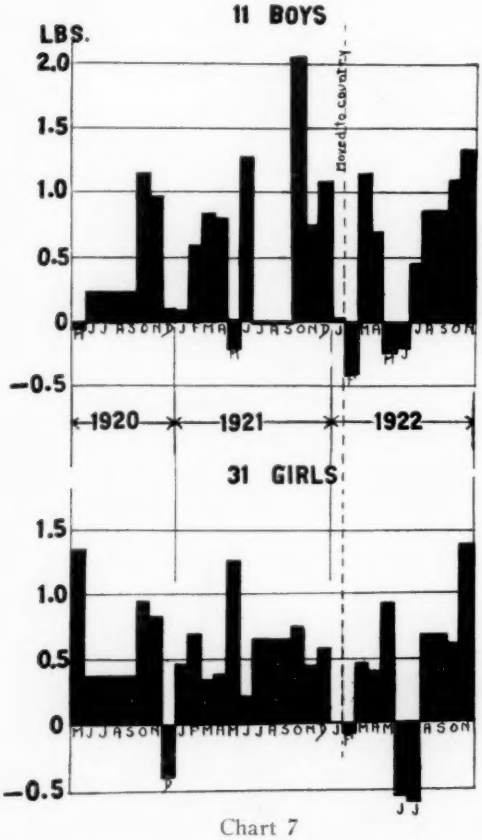

Chart 7

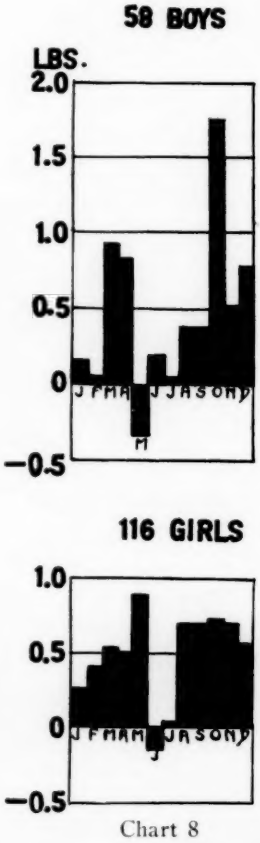

Chart 8

Chart 7.—Average monthly weight gain in children observed for thirty-one months.

Chart 8.—Average monthly weight gain in children observed for one year.

considering these observations, the fact that we have grouped together children of different ages does not vitiate any conclusions, since the same children were observed throughout the entire period.

Chart 8 gives the average increment in weight for each calendar month for fifty-eight boys and for 116 girls who were under observation continuously for one year.

It seems quite clear that it cannot be laid down as a rule that a healthy child gains a certain amount each month, nor that at any particular month or period the increase in weight is regularly more rapid, and at another period regularly slower, than the average rate for the year. The tendency, however, is certainly toward a more rapid gain in the autumn months. The fact that the children studied by us, in regard to whom seasonal differences in diet and environment were insignificant, showed a marked, but irregular variation in monthly gain, would seem to indicate that the seasonal variation found by others is not due chiefly to the factors mentioned. It seems probable that a difference in activity may account for some of the difference between the summer and autumn gains, since the marked activity of the vacation months is usually reduced when the children spend four or five hours a day in school.

The one thing which was found to be fairly regular in these children was the annual increment. This was quite uniform. In this respect, our observations are in close accord with those of others. The regularity of the annual increment is of great significance in establishing a standard for healthy growth.

It seems of interest to append a few individual growth charts which are typical of certain groups of the children studied.

Chart 9 shows the growth curves for two years of a girl, 10 years old at the beginning of observation, who was of average weight for height and average size for age. The net progress in both weight and height in the two years proceeded at the normal rate, although there were marked fluctuations in weight, there being several periods of four or five months in which no net gain occurred. It will be noted that these periods of slow gain had no regular relation to season.

Chart 10 shows the growth curves for two and a half years of a girl, 8 years and 6 months old at the beginning of observation, who was at that time of average weight for height and average size for age, but who grew at better than the average rate. The fluctuations in the weight gain are especially marked. There are two periods in which there was continuous weight loss for about five months, followed, however, by a rapid gain in weight. This case illustrates especially the possible fallacy in judging the condition of the child and the progress in nutrition by following the weight for a short time.

Chart 11 shows the growth of a boy, 9 years and 6 months old at the beginning of observation, followed for two years, who was of average weight for height and a little more than average size for age, and whose growth proceeded at about the usual rate. Especially noteworthy is the marked drop in weight without evident cause in June and July of the second year, followed by a rapid increase which more than compensated for the decline.

Chart 12 shows the growth of a boy, 11 years old at beginning of observation, followed for over two years. He was undersize for his age at the beginning of observation, and grew at considerably more than the average rate. The progress in this case was regular. This case, like the others presented, illustrates especially the fact that gains in weight and height usually proceed together.

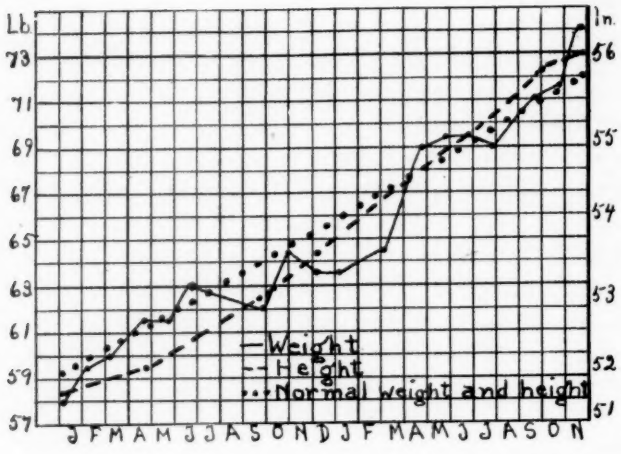

Chart 9.—Gain in weight and height of A. P., girl, French (initial age, 9 years and 11 months).

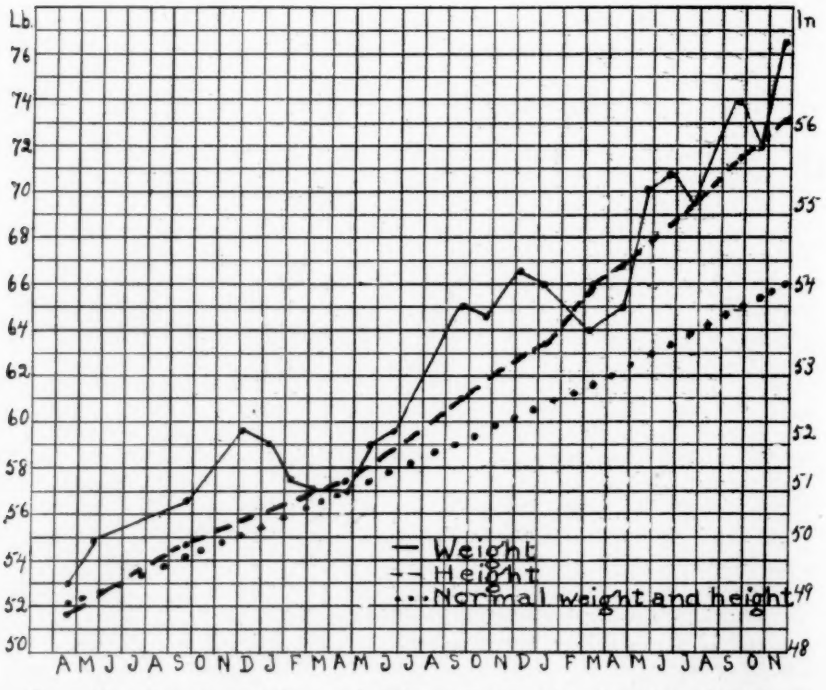

Chart 10.—Gain in weight and height of E. M., girl, Austrian (initial age, 8 years and 5 months).

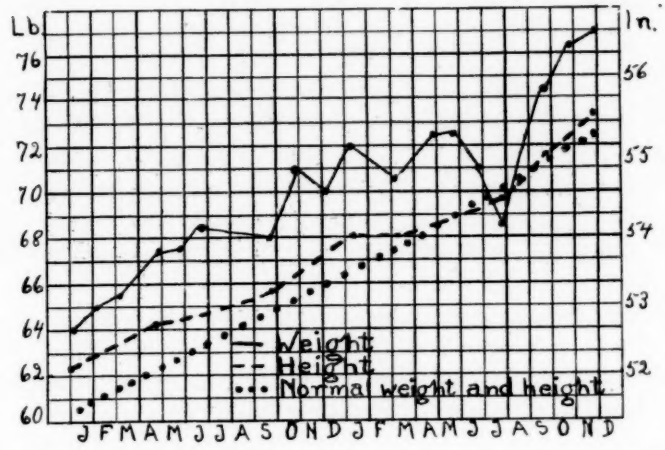

Chart 11.—Gain in weight and height of M. C., boy, French (initial age, 9 years and 8 months).

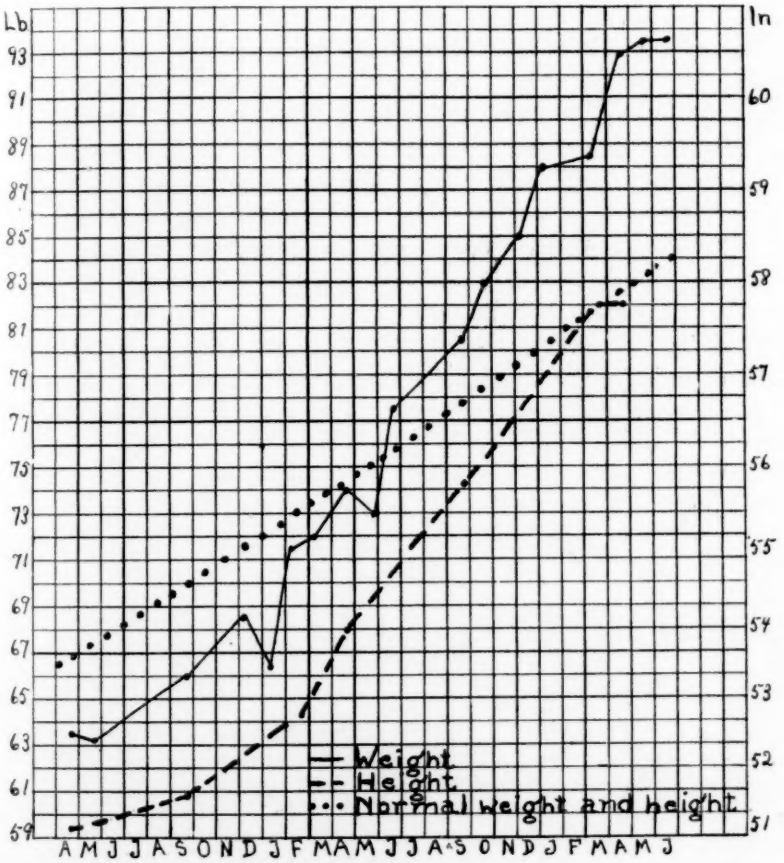

Chart 12.—Gain in weight and height of D. C., boy, Italian (initial age, 10 years and 10 months).

SUMMARY

1. The observations show that strikingly good health and excellent nutrition can be maintained in an institution. The factors which contributed to this result were: (1) regularity in habits of eating and in sleep, rest and exercise; (2) a liberal but simple diet, and (3) freedom from contact infections. This shows what might be the case in private families provided the same rules of simple and regular living were observed.

2. In the distribution of fat, protein and carbohydrate in the diet, there existed a considerable deviation from what is considered optimum. In spite of this, health and digestion remained excellent, and the gains in weight were satisfactory. This shows how wide a deviation is consistent with health, provided certain essentials in the diet are furnished, and that regularity in habits is maintained.

3. Growth possibly would have been better if more milk had been allowed, furnishing more fat, more vitamin A and more calcium.

4. The usually accepted standard for normal nutrition, that is, inclusion in this group of those who were not more than 10 per cent. below the average weight for height, was found to hold good when applied to these children in spite of the differences of nationality.

5. While these observations are not numerous, they were continued long enough to show very clearly that in this group there were no regular seasonal variations. This is especially significant since the living conditions were so nearly uniform throughout the year.

6. The annual rate of gain was remarkably regular, though the monthly gains showed wide fluctuations, with no regularity whatever. This emphasizes the necessity of prolonged observations before a stationary weight can be considered significant.

THE LEUKOCYTE COUNT IN THE NEW-BORN WITH DEHYDRATION FEVER*

HARRY BAKWIN, M.D., AND RUTH M. MORRIS, M.D.
NEW YORK

The purpose of these observations was to determine whether or not an increase in the leukocyte count accompanies the transient fever which frequently occurs in the new-born during the first week of life. It has long been thought that this fever may be due to dehydration. Holt,[1] in 1895, pointed out that it occurred in infants who had lost a great deal of weight (a part of which, presumably, is due to water loss), and that it could be cured by the administration of fluids. In a recent paper,[2] it was shown that the transient fever of the new-born is associated with a decrease in the plasma water, as indicated by an increase in the protein concentration of serum, determined refractometrically. The oral administration of warm water results in a drop in the temperature to normal within from thirty to ninety minutes. This is accompanied by an increase in the water content of the blood, as shown by a fall in the serum protein concentration and the red cell count.[3] In infants with fever due to infections, the serum proteins are not increased, and no significant fall in temperature follows water gavage despite the fact that this procedure is followed by an increase in the blood water.

Bacon, Novy, and Eppler[4] in a study of the leukocyte count in dehydration fever in animals, induced fever by rapidly injecting hypertonic salt solutions into the femoral vein of dogs after the manner described by Balcar, Sansum and Woodyatt.[5] At the end of the first hour, they found a slight leukopenia with a relative increase of the small lymphocytes. Following this there was a steady rise in the leukocyte count to levels far above normal. The increase was almost wholly confined to the polymorphonuclear leukocytes.

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* Received for publication, May 5, 1923.

* From the Pediatric Division of the New York Nursery and Child's Hospital, and the Department of Pediatrics, Cornell University Medical College.

1. Holt, L. E.: Inanition Fever in the Newly Born, Arch. Pediat. **12**:560, 1895.

2. Bakwin, Harry: Dehydration Fever in the New-Born, Am. J. Dis. Child. **24**:508 (Dec.) 1922.

3. Bakwin, Harry; Morris, R. M., and Southworth, J. D.: To be published.

4. Bacon, D. K.; Novy, F. O., and Eppler, H. H.: Factors in Leukocytosis, Arch. Int. Med. **30**:229 (Aug.) 1922.

5. Balcar, J. O.; Sansum, W. D., and Woodyatt, R. T.: Fever and Water Reserve of the Body, Arch. Int. Med. **24**:116 (July) 1919.

Bacon and his co-workers point out the similarity in the leukocytic reaction in experimentally produced dehydration fever and in the fever following the injection of a foreign protein. They believe that the mechanism by which fever and leukocytosis are produced is identical in both conditions. According to them, the acute water shortage in

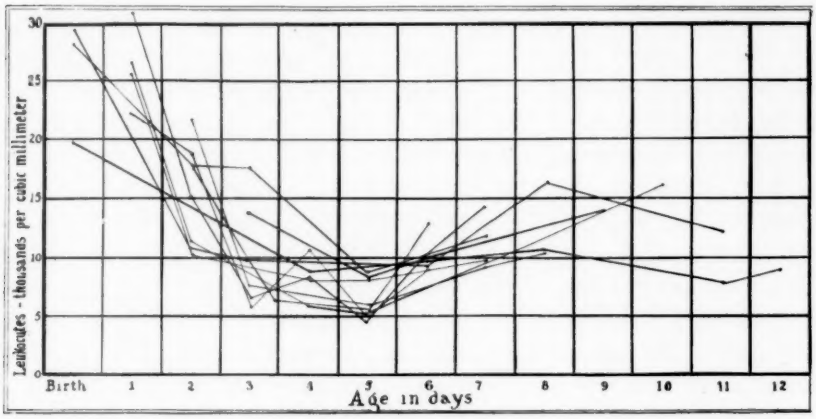

Chart 1.—Variations in the leukocyte count of afebrile new-born infants during the first few days of life.

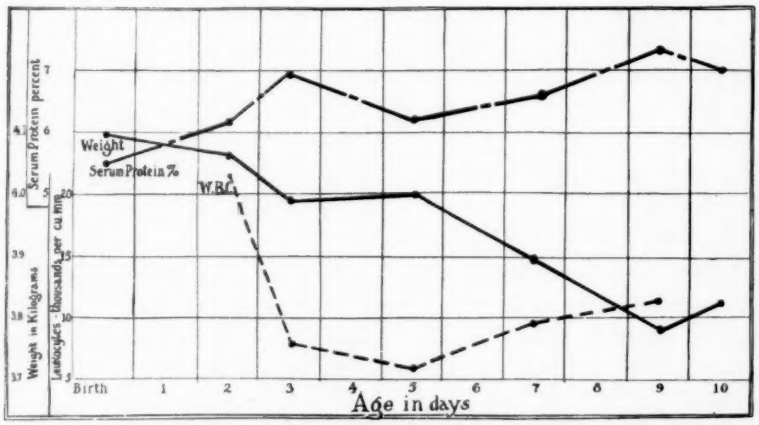

Chart 2.—The lack of relationship between variations in blood concentration and the leukocyte count is shown. As the weight falls, the percentage of serum protein rises, indicating a diminution in the plasma water. The increase in weight is accompanied by a return of the serum proteins to normal. The physiologic drop in number of the leukocytes occurs during the first five days, despite the increase in blood concentration.

dehydration fever results in an accelerated protein metabolism with the greater productions of its by-products, such as urea and creatinin. As evidence for this hypothesis, they point to the rise in the nonprotein

nitrogenous constituents of the blood that occurred regularly in their dogs with dehydration fever.

Rietschel [6] has recently called attention to a nonbacterial form of fever which he calls "dynamisches Eiweissfieber." He produced it in infants by feeding concentrated diets of high protein content, and

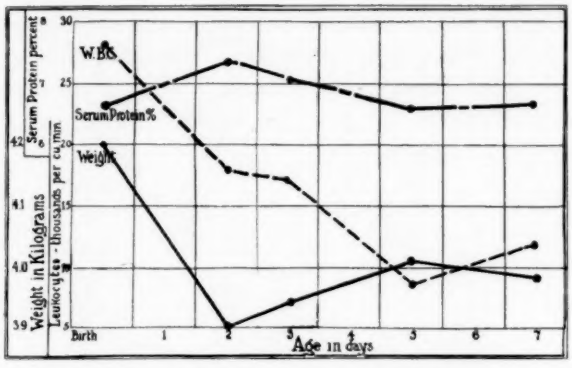

Chart 3.—The lack of relationship between variations in blood concentration and the leukocyte count is shown. The fall in leukocytes during the first week and the slight rise during the second week are entirely independant of the blood concentration, as measured by variations in the percentage of serum protein.

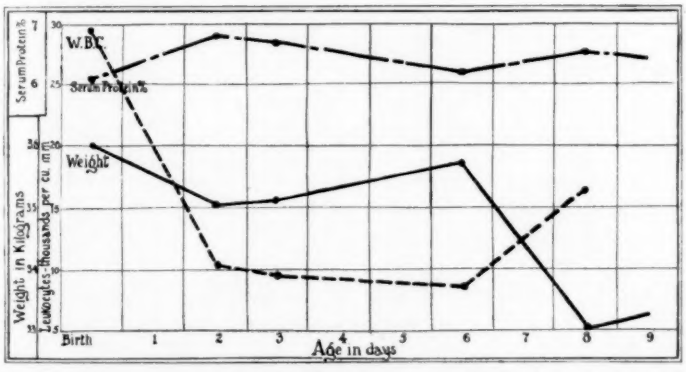

Chart 4.—The lack of relationship between variations in blood concentration and the leukocyte count is shown. The fall in the number of leukocytes during the first week and the slight rise during the second week are entirely independent of the blood concentration, as measured by changes in the percentage of serum protein.

he ascribes it to the increased metabolism resulting from the high specific dynamic action of protein. Because of the low fluid content of the diet, sufficient water is not available for the elimination of the

6. Rietschel: Dynamisches Eiweissfieber, Klin. Wchnschr. **2**:9 (Jan. 1) 1923.

increased amount of heat from the body surface by evaporation. (Somewhat similar examples of fever of nonbacterial origin in infants have been described by Finkelstein,[7] Holt and Levene [8] and Benjamin.[9])

No figures are available concerning the leukocyte count in new-born infants with dehydration fever. Repeated determinations were made on a large series of infants during the first ten days of life. Blood was obtained from the toe from three to four hours after a feeding, and counts were made in the usual manner. Blood for serum protein concentration was collected at the same time. The technic employed was similar to that described in previous papers.[10] The temperature was taken at the time of puncture.

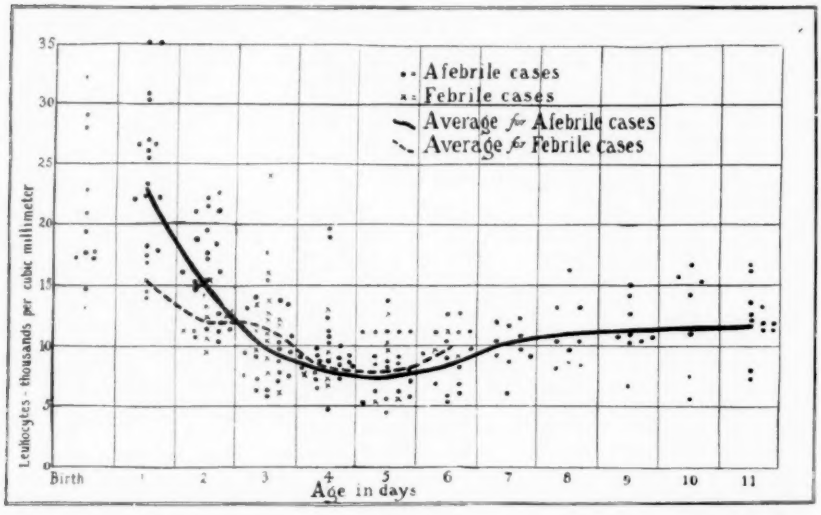

Chart 5.—The leukocyte count in afebrile and febrile new-born infants. The average curves are almost identical.

Because of the wide variations in the number of leukocytes during the first weeks of life, a group of afebrile babies was studied. Our results correspond fairly closely to those of previous observers.[11] On the first day (Table 1 and Chart 1), the white cells are markedly

7. Finkelstein, H.: Ueber alimentärisches Fieber, Deutsch. med. Wchnschr. **35**:190, 1909.

8. Holt, L. E., and Levene, P. A.: The Influence of High Protein Feeding on the General Metabolism, on the Intestinal Flora, and on the Body Temperature of Infants, Am. J. Dis. Child. **4**:265 (Nov.) 1912.

9. Benjamin: Weitere Untersuchungen zum Eiweissnährschäden des Säuglings, Jahrb. f. Kinderh. **80**:545, 1914.

10. Bakwin, Harry: Dehydration in the New-Born, Am. J. Dis. Child. **24**:497 (Dec.) 1922.

11. Von Reuss, A. R.: Diseases of the New-Born, London, 1921, p. 42.

increased in number, usually ranging between 20,000 and 25,000 per cubic millimeter. They fall rapidly and reach the adult level on the fifth to the seventh day. A rise to 10,000 or 12,000 follows, during the second week.

It has been suggested that the leukocytosis in the new-born is due to an increase in the blood concentration. Repeated simultaneous observations on the white cell count and the serum protein concentration show that the variations in the leukocytes are entirely independant of

TABLE 1.—*Daily Variations in the Leukocyte Counts in Afebrile and Febrile New-Born Infants*

	Afebrile				Febrile			
Age, Days	Number of Cases	Leukocytes per C.Mm.			Number of Cases	Leukocytes per C.Mm.		
		Maximum	Minimum	Average		Maximum	Minimum	Average
Birth	12	32,400	17,200	20,300	0	.....	.....	.....
1	19	35,400	16,800	22,500	1	15,400	15,400	15,400
2	21	22,000	10,400	15,600	7	14,300	9,500	12,100
3	21	17,700	5,700	10,000	15	24,000	6,000	12 500
4	23	19,000	4,800	9,300	5	13,000	6,600	8,700
5	20	13,600	4,500	7,800	5	12,900	5,500	8,700
6	15	12,900	5,200	9,200	3	11,200	9,500	10,100
7	10	12,100	6,000	10,200				
8	9	16,300	8,000	10,600				
9	9	15,000	6,600	10,800				
10	7	16,200	5,700	12,100				
11	12	16,500	7,300	12,300				
12	4	19,900	9,100	12,500				

TABLE 2.—*Temperature and the Leukocyte Count in New-Born Infants*

Temperature		Number of Cases	Leukocytes per C.Mm.		
Centigrade	Fahrenheit		Maximum	Minimum	Average
36.1	97	34	30,800	4,800	10,800
36.6	98	139	35,400	5,400	11,800
37.2	99	35	22,400	7,200	13,200
37.8	100	15	24,000	5,500	11,000
38.4	101	8	15,400	9,500	11,900
38.9	102	10	15,900	6,000	11,300
39.5	103	5	16,100	7,600	12,100

changes in the blood concentration determined refractometrically (Charts 2, 3 and 4).

The daily leukocyte counts in new-born infants with and without fever are presented in Table 1. It will be seen that the daily variations in the white cell counts of babies with fever correspond closely to the variations of those without fever. This is graphically represented in Chart 5.

In Table 2, the leukocyte counts are arranged according to the temperature. No relationship was found between the degree of fever and the leukocyte count.

SUMMARY AND CONCLUSIONS

1. At birth, the leukocytes are increased, the counts usually ranging between 20,000 and 25,000 per cubic millimeter.

2. There is a rapid fall to normal during the first week, followed by a rise, usually starting on the fifth day, to from 10,000 to 12,000.

3. The variations in the leukocyte count are not due to changes in the blood concentration.

4. There is no change in the leukocyte count in new-born infants with dehydration fever, the daily average in those with fever corresponding closely to that in babies without fever.

THE BASAL METABOLISM OF PREMATURITY

III. METABOLISM FINDINGS IN TWENTY-ONE PREMATURE INFANTS *

FRITZ B. TALBOT, M.D.; WARREN R. SISSON, M.D.;
MARGARET E. MORIARTY, S.B.,

AND

ALICE J. DALRYMPLE

BOSTON

The object of the present study, commenced two years ago, was to gain further knowledge of the premature infant, and, if possible, to establish the physiologic basis for the nutritional requirements of these infants.

A review of the literature showed that few studies had been made on the metabolism of premature infants. Some of these studies cannot be accurately interpreted because of differences in technical methods. This is particularly true of Rubner and Langstein's [1] and Weiss' cases.[2] The investigations of Hasselbalch,[3] although carried out with a slightly different technic, are comparable, because they were obtained under basal conditions. The cases reported by Fleming, Murlin and Marsh [4] and Benedict and Talbot [5] are strictly comparable. So far as we know, there have been no comprehensive studies of the basal metabolism of prematurity before the present series and the one subsequently reported by Murlin. Most of the data in Table 1 appear in scattered publications incidental to other pieces of work. The results of these investigations are also recorded in the table.

A study of the figures of the heat production per unit of body surface in the table shows a wide variation in results. Rubner and Langstein's findings are much higher than those of the other investigators and presumably do not represent basal figures. The striking feature brought out by the results of the other investigators is the very low heat production of the premature infant.

The series reported below includes determinations of the basal metabolism of twenty-one premature infants. Some of the results have already been published in preliminary reports.[6]

* Received for publication, April 19, 1923.

* From the Children's Medical Department, Massachusetts General Hospital.

1. Rubner and Langstein: Arch. f. Physiol., 1915, p. 39.
2. Weiss: Bull. de l'Acad. de méd., Paris **60**:458, Series 3, 1908.
3. Hasselbalch: Respirationsforsøg paa nyfødte Børn, Bibliot. f. Læger **8**:219, 1904.
4. Murlin and Marsh: Proc. Soc. Exper. Biol. & Med. **19**:431, 1922.
5. Benedict and Talbot: Pub. 233, Carnegie Institute, Washington.
6. Talbot, F. B., and Sisson, W. R.: Proc. Soc. Exper. Biol. & Med. **19**:309, 1922. Talbot, F. B.; Sisson, W. R.; Moriarty, Margaret, and Dalrymple, Alice: Basal Metabolism of Prematurity, II, Relation of Basal Metabolism to Caloric Intake and Weight Curve, Am. J. Dis. Child. **24**:95 (Aug.) 1922.

CLINICAL MATERIAL

The infants studied in this series, twenty-one in number, were patients at the Boston Lying-In Hospital and the Massachusetts General Hospital. The criteria used for establishing prematurity were weight, length, and general characteristics, such as facies, texture of the skin, undeveloped nails, cry, unstable temperature and history of expected birth. It was impossible in many instances to determine the exact date of the expected birth, but only such babies were selected for study who were at least from four to ten weeks premature. The actual stage of fetal life is difficult to estimate from either the physical examination or the mother's history. The estimates that have been made

TABLE 1.—*Previous Investigations on the Metabolism of Premature Infants*

Author	Age, Days	Sex*	Weight, Gm.	Height, Cm.	Respiratory Quotient	Heat Produced in 24 Hrs. Total	Per Kilogram	Per Sq. M. $10\sqrt[3]{Wt.^2}$	Remarks
Hasselbalch [3]									
Case 5	2	♀	1,825	44	0.87	67.3	36.9	448	Died on third day
Case 15	5	♀	1,900	..	0.77	57.8	30.4	366	
Case 16	5	♀	1,900	..	0.81	63.9	33.6	404	
Weiss [2]									
Case 5	6	♂	1,530	..	0.70	82.8	54.0	606	
Case 8	6	♀	1,850	..	0.76	96.9	52.4	624	
Case 12	1	♂	1,950	..	0.81	93.1	47.7	579	
	3	..	1,800	..	0.82	96.9	53.8	636	
	5	..	1,800	..	0.83	92.1	50.0	591	
Benedict and Talbot [5]									
Case 24	20½ hr.	♂	2,350	43	0.77	81.0	35.0	445	1 to 2 months premature; died subsequently of inanition
Rubner and Langstein [1]									
Case Koza	10	..	2,050	44	....	....	....	973	1+ month premature
Case Goerz	4	..	.....	45	....	....	....	1,032	1 month premature
	6	..	.....	..	....	....	....	956	
Fleming	21	..	2,320	50	0.86	143.0	66.4	798	1 month premature

* In this column, ♀ indicates female; ♂, male.

are based in most instances upon the obstetrician's prenatal examination and upon the date of the expected birth as given by the mother. In the majority of instances, the babies weighed less than 2 kilograms, were unable to nurse at the breast and had subnormal temperatures for the first few days of life. The low body temperatures were often raised with difficulty even though the babies were kept in a room at from 75 to 80 F., and received the usual care of premature cases. Hot water bottles were constantly kept in the bed and the infants wore suitable jackets.

The food consisted chiefly of human milk. At times, it was necessary to substitute modified cow's milk.

The clinical development of these babies can best be shown by reference to their weight curves, seven of which have already been

published.[7] In Charts 1-14, inclusive, typical curves of the remaining infants of the series are shown. It will be noted that, in most instances, there was a period of stationary weight lasting for seven to ten days; but following this the development was generally satisfactory during the period of observation. The failure of these infants to gain during the first few days of life can be explained by frequent regurgitation and vomiting of food and mucus, and by the fact that human milk was unobtainable at the time. The weight curves show that in some

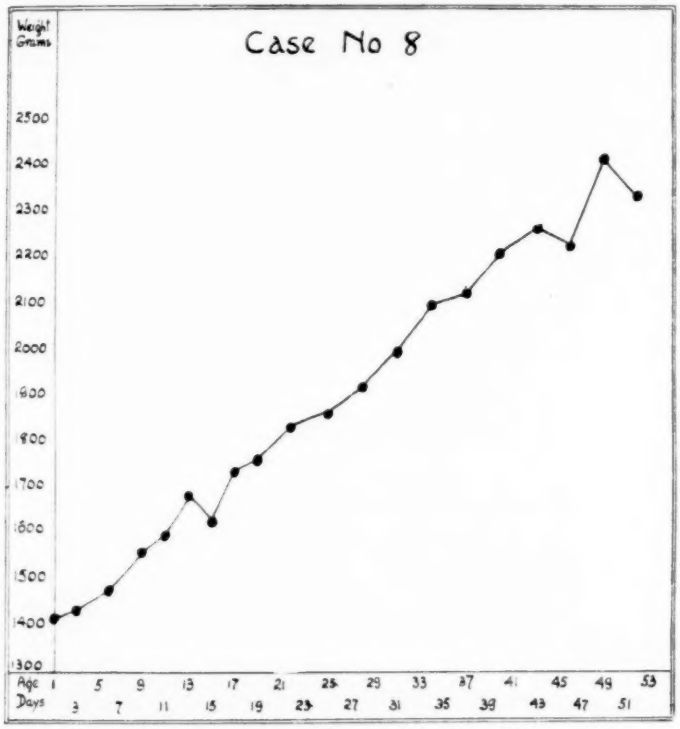

Chart 1.—Weight curve of premature infant.

instances there was no gain for from seven to ten days, but after this time most of the infants studied gained during the six to twelve weeks of observations. The characteristic weight curves are shown in Charts 1-14.

The weight curve of Cases 1-7 inclusive may be found in an earlier report.[7] It was noted that in most instances the babies that had subnormal temperatures showed a slower initial gain than those that could easily be kept at normal body temperature, but eventually

7. Talbot et al.: Footnote 6, second reference.

devolped satisfactorily. Complete physical examinations were made of all infants in this series, and abnormalities were recorded. The Wassermann reaction of the placental blood was negative in all instances except Case 8, in which the infant was congenitally syphilitic.

Table 2 gives the birth weight of these infants, with as accurate an estimation of their prematurity as was possible.

PROCEDURE

The baby was carried from the Boston Lying-In Hospital in a padded basket, surrounded by hot water bags. Before the laboratory was reached, the water in the bath surrounding the respiratory chamber was warmed to between 26 and 28 C., and the room itself was warmed

TABLE 2.—*Birth Weight and Amount of Prematurity of Series of Premature Infants*

Case	Sex*	Estimated Prematurity, Days	Birth Weight, Gm.
1	♀	64	1,616
2†	♂	59	1,630
3†	♂	59	
4†	♂	59	1,814
5†	♀	59	1,814
6	♀	54	1,814
7	♀	46	1,654
8	♀	60	1,814
9	♀	14	1,899
10	♂	48	1,711
11	♂	68	1,191
12	♀	44	1,927
13	♂	43	1,814
14	♀	60	2,098
15†	♀	61	1,630
16†	♀	61	1,630
17	♂	108	1,654
18	♂	60	1,810
19	♂	60 ?	1,361
20	♂	60	.....

* In this column, ♀ indicates female; ♂, male.
† Twins.

to the same or a higher temperature. The infant was placed in the chamber wrapped in blankets, the cover lowered and, after the thermometers were inserted, the ventilation started. Great pains were taken to keep the room temperature as high as the temperature within the chamber, both for the accuracy of the measurements, and for the even maintenance of the infant's environment. The infant was fed immediately before observation was commenced.

A preliminary period of from half to three quarters of an hour, which was always disregarded, passed before the actual determination. When the temperatures in the chamber became constant, the measurements were commenced, and the length of the period varied from seventy-five minutes to two hours, depending on the size of the infant and the amount of carbon dioxid eliminated. In no case could the

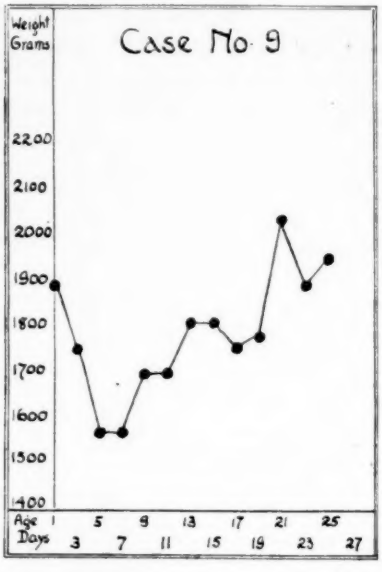

Chart 2.—Weight curve of premature infant.

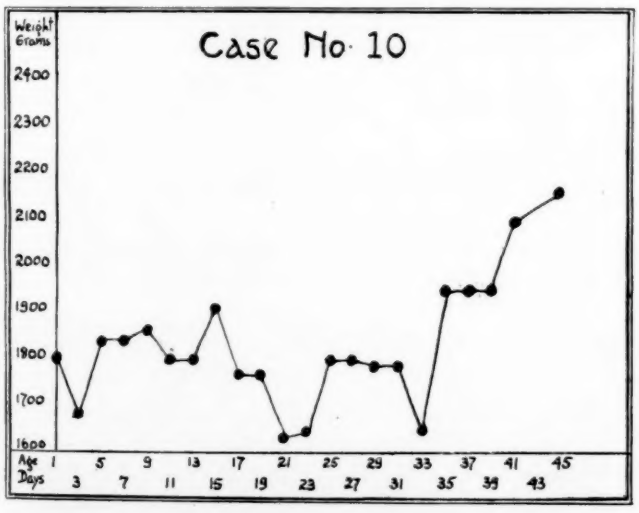

Chart 3.—Weight curve of premature infant.

period be continued longer than two hours without interfering with the feedings, which were given every three hours.

If the temperature of the respiratory chamber started to fall during the period, it could be raised again by means of two electric water heaters placed in the bath surrounding the chamber. It was invariably necessary to use the heater toward the close of the period to maintain the temperature of the chamber at the same level as at the beginning of the period. The experiment was ended in the manner previously described.[8] It was frequently impossible to record the pulse rate of these infants because they were so small that a stethoscope could not

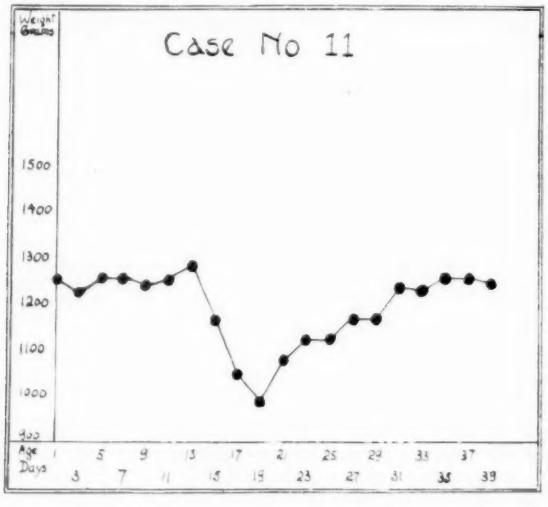

Chart 4.—Weight curve of premature infant.

be attached to the chest. It was impractical to make electric cardiographic records. Consequently, the pulse rate has only been recorded in a few instances.

In all cases, the body temperature of the infants was the same or slightly higher at the end of the period than before entry into the chamber.

Some of the data obtained during the first month of this investigation was subjected to severe criticism because of the small amounts of oxygen and carbon dioxid measured. As a result, the respiratory quotients of many observations were discarded. A number of alcohol checks were run to determine the smallest amount of carbon dioxid and oxygen that would give an accurate respiratory quotient, and the conclusion was reached that any amount appreciably less than 1 liter of

8. Benedict and Talbot: Pub. 201, Carnegie Institute, Washington.

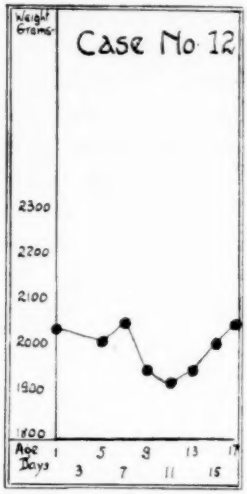

Chart 5.—Weight curve of premature infant.

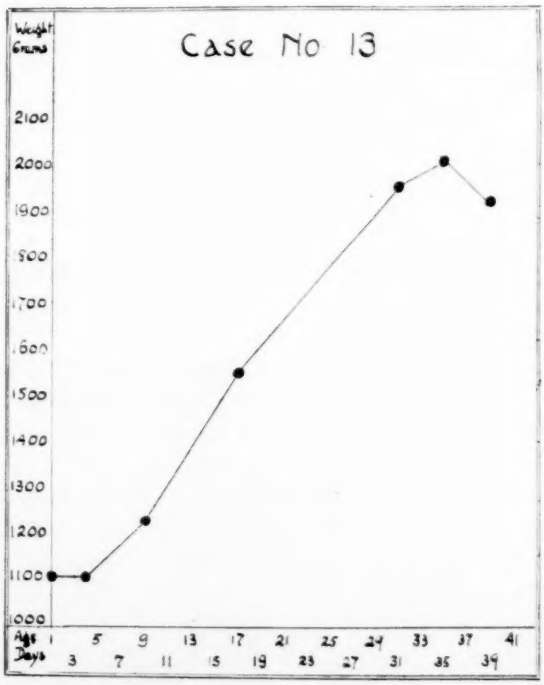

Chart 6.—Weight curve of premature infant.

oxygen and less than 1.4 grams carbon dioxid could not be depended on to give reliable respiratory quotients.[9] In those cases in which the measured amount of carbon dioxid and oxygen was lower than these minimum amounts, an average respiratory quotient was used in calculating the heat production from carbon dioxid. This quotient was obtained by averaging the quotients found in the infants that consumed enough oxygen and produced enough carbon dioxid to be above the selected minimum.

The average respiratory quotient of this series of premature infants was 0.96. This would seem to indicate that the principle source of their heat was carbohydrate. The respiratory quotient of the new-born

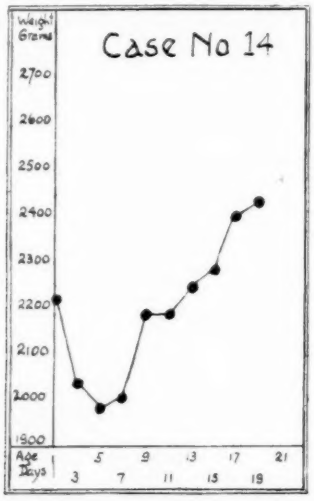

Chart 7.—Weight curve of premature infant.

infant determined in a large series of cases [5] was found to change during the first few days of life, falling quite rapidly after birth until the third day of life, when it reached its lowest, averaging 0.73. At this time, food influenced the quotient; it commenced to rise, and on the eighth day reached 0.80. During later infancy, it ran somewhat higher, and was occasionally above 0.90, even after the ingestion of food. In the adult, the postabsorptive quotient is 0.81.

Although the conclusion was reached that less than 1.4 gm. of carbon dioxid is not a large enough amount from which to estimate the respiratory quotient, it seems justifiable to use as small an amount as 1 gm. of measured carbon dioxid in estimating the heat production. During the early stages of the research, consideration was given to the

9. Unpublished data.

probability of error when small amounts of carbon dioxid were measured. This was found to be less than was expected. It is shown in the figures of carbon dioxid excretion of premature twins and of two premature triplets measured separately and together, and also in cases in which several measurements were made on the same infant on the same or successive days. These are recorded in Table 3.

These figures show that even with very small amounts of carbon dioxid it is possible to obtain accurate results (A1 and A2). Table 4 also shows very close agreement. Even with the greater error in P2

TABLE 3.—*Carbon Dioxid Production of Twins, Separately and Together*

Case	Age, Days	Carbon Dioxid per Hour, Gm.
P2 and P3, together	18	1.93
P2, singly	16	1.31
P3, singly	16	0.98
		2.29
A1, singly	10	0.83
A2, singly	10	0.74
		1.57
A1 and A2, together	11	1.59

TABLE 4.—*Carbon Dioxid Production of Premature Infants on the Same Day or on Successive Days*

Case	Date	Carbon Dioxid Production per Hour, Gm.
18 (Table 5)	3/22/20	1.43
	3/23/20	1.46
	3/24/20	1.43
8 (Table 5)	1/25/22	1.11
	1/26/22	1.11
	1/27/22, a. m.	1.28
	1/27/22, p. m.	1.30
	2/ 7/22, a. m.	1.32
	2/ 7/22, noon	1.39
	2/ 7/22, p. m.	1.37

and P3, the final table and charts show such uniformity in the general trend of the metabolism that the error which might be present in very small premature infants cannot have affected the results to any great degree.

Table 5 gives the basal metabolism findings in a series of the twenty-one premature infants studied.

COMMENT

The usual custom of charting the values in relation, first to age, then to body weight and finally to body surface has been followed. Since the work of Benedict and Talbot [10] has shown that there is little or

10. Benedict and Talbot: Pub. 302, Carnegie Institute, Washington.

no sex differentiation below the weight of 11 kg., these cases have not been charted by sex.

Each point on the charts represents a separate metabolism determination, but not a different subject in all cases. In some instances, determinations were made on the same child at different ages. In Case 6, the metabolism was determined nine times at different ages, covering in all a period of three months. The metabolism in Case 8 was determined on three successive days, on the last of which observations were made in the morning and the afternoon. Reference to the table shows how

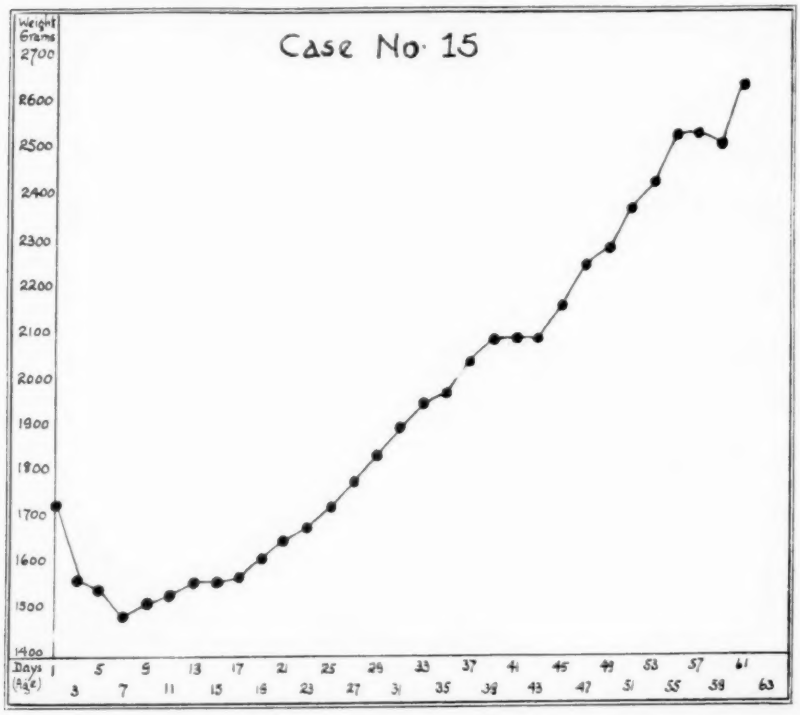

Chart 8.—Weight curve of premature infant.

closely these figures correspond, and speak again for the accuracy of the results. When the metabolism was determined on successive days, it was averaged and placed on the chart as a single dot.

GENERAL TREND OF THE METABOLISM WITH INCREASING AGE

The total calories for twenty-four hours, as referred to age, have been outlined in Chart 15, which shows that there is a gradually increasing heat production with increasing age. The lowest heat production was found in the first ten days of life (Cases 1, 3, 4, 11).

TABLE 5.—*Basal Metabolism Findings in a Series of Twenty-One Premature Infants*

TABLE 5.—*Basal Metabolism Findings in a Series of Twenty-One Premature Infants*

Case	Age, Days	Date	Weight, Kg.	Height, Cm.	Sitting Height, Cm.	Length of Period, Min.	Oxygen Measured,* Gm.	Carbon Dioxid Measured, Gm.	Carbon Dioxid per Hour, Gm.	Respiratory Quotient	Total Calories	Calories per Kilogram	Calories per Square Meter		Activity	Pulse Rate	Temperature of Baby (Fahrenheit)		Temperature of Box (Centigrade)	
													DuBois	Benedict and Talbot			Before	After	Before	After
1	4	2/14/22	1.418	....	....	97	.....	1.17	0.72	0.96†	46.0	32.5	.....	361.1	I	...	98.1	.....	28.23	28.44
	6	2/16/22	1.432	42.0	28.0	92	.....	1.35	0.88	0.96†	56.0	39.2	462.8	436.8	I	...	98.8	.....	28.15	28.31
2	16	1/31/22	1.644	46.0	28.0	92½	0.972	2.02	1.31	1.06	80.8	49.1	535.0	580.0	I	...	99.0	99.0	28.47	28.60
	33	2/17/22	2.155	47.0	30.5	96	1.770	3.39	2.19	0.98	132.8	61.6	785.0	795.2	I	...	98.9	.....	29.99	29.75
3	16	1/31/22	1.474	42.5	26.5	96½	0.964	1.58	0.98	0.83	70.0	47.5	485.8	540.0	I	...	98.8	.....	29.78	28.44
	34	2/18/22	1.843	42.5	29.1	97	1.460	3.00	1.86	1.05	114.4	62.1	747.8	761.1	I	...	99.0	.....	29.77	30.27
4	10	2/ 1/22	1.757	42.5	28.0	109	.....	1.50	0.83	0.96†	52.5	29.9	394.8	360.7	I	...	99.0	.....	26.47	26.54
	24	2/15/22	1.673	45.5	28.5	94½	.....	2.43	1.54	0.96†	98.1	58.7	663.0	696.0	I	...	98.8	.....	28.52	28.40
5	10	2/ 1/22	1.644	43.0	27.0	101½	.....	1.25	0.74	0.96†	47.0	28.6	330.9	334.0	I	...	98.1	98.2	29.93	29.87
	25	2/16/22	1.970	46.8	29.2	99¼	1.280	2.41	1.46	0.96	92.7	47.0	648.0	583.8	I	...	98.8	.....	28.02	28.79
6	9	11/10/21	1.616	....	....	53	.....	1.10	1.25	0.96†	79.2	49.0	.....	569.4	I+	156	98.8	99.2	29.05	28.76
	11	11/12/21	1.715	....	....	72	.....	1.29	1.08	0.96†	68.4	39.9	.....	472.5	I	146	98.8	100.0	30.98	30.28
	15	11/16/21	1.772	43.8	29.0	87½	.....	1.42	0.97	0.96†	61.9	35.0	430.1	418.7	I	...	99.0	99.3	27.10	26.83
	30	12/ 1/21	1.814	....	....	65½	.....	1.21	1.11	0.96†	70.5	38.9	.....	469.3	I+	...	99.0	98.8	29.24	28.89
	45	12/15/21	2.098	....	....	86½	1.050	2.39	1.66	0.90†	105.4	50.3	.....	637.0	I	127	98.8	99.8	33.52	32.24
	50	12/20/21	2.183	....	....	66½	1.110	2.14	1.93	0.98	120 9	55.4	.....	711.3	I	...	99.0	.....	30.66	30.46
	58	12/28/21	2.381	....	....	49½	1.160	2.04	2.47	0.90	165.3	69.4	.....	917.7	I	110	99.4	98.0	31.25	31.00
	64	1/ 5/22	2.495	47.0	31.8	53½	.....	1.93	2.16	0.96†	137.7	55.2	769.1	740.9	I	...	98.6	.....	28.99	28.75
	97	2/ 8/22	3.019	53.0	34.0	75	2.060	3.84	3.07	0.95	196.9	65.2	911.7	933.5	I	...	.....	.....	23.90	23 83
7	14	11/29/21	1.559	....	....	69	.....	1.34	1.17	0.96†	75.8	47.5	.....	545.7	I	...	100.4	99.5	30.43	30.16
	23	12/ 8/21	1.616	47.0	29.5	91½	.....	1.63	1.07	0.96†	68.0	42.1	539.5	488.8	I	...	99.2	99.3	31.00	30.28
	45	12/30/21	1.942	....	....	65	.....	1.41	1.30	0.96†	82.8	42.6	.....	526.5	I	151	98.6	.....	31.35	29.72
	65	1/19/22	2.467	48.8	35.4	89½	1.620	3.30	2.21	1.04	136.4	55.3	762.0	739.7	I	...	98.6	99.3	29.70	29 98
8	15	1/25/22	1.474	....	....	80	.....	1.48	1.11	0.96†	70.6	47.9	.....	539.7	I	...	100.0	99.6	28.81	29.11
	16	1/26/22	1.559	....	....	69½	.....	1.28	1.11	0.96†	70.3	45 1	.....	513.4	I	...	99.2	100.2	29.39	28 29
	17	1/27/22	1.559	....	....	68	.....	1.45	1.28	0.96†	81.4	52.2	.....	599.2	I	...	98.0	98.2	26.92	26.62
		1/27 p.m.	1.559	....	....	92	1.040	2.00	1.30	0.98	81.7	52.4	.....	601.4	I	...	99.6	99.8	26.91	27 82
		2/ 7/22	1.814	45.0	30.5	146	1.630	3.20	1.32	1.00	81.1	44.7	523.1	539.7	I	152	99.0	98.6	28.43	29 24
		2/ 7/22	.....	....	....	164	2.060	3.80	1.39	0.94	89.9	49.6	580.1	598.6	I	152	98.6	98.8	28.76	28.34
		2/ 7/22	.....	....	....	184	2.640	4.19	1.37	0.81	99.2	54.7	640.0	660.3	I	152	98.8	98.6	28.05	28 41
9	11	11/23/22	1.701	43.5	28.5	92	0.960	1.71	1.12	0.88	75 9	44.6	583.8	526.9	I	...	98.2	99.4	26.89	26.68
	23	12/ 5/22	1.928	44.5	29.1	87	1.390	2.63	1.81	0.96	115.4	59.8	769.0	737.3	I	...	98.8	99.4	28.23	27.57
10	6	2/ 6/22	1.729	43.0	26.2	91	.....	1.94	1.28	0.96†	81.4	47.1	707.4	564.8	I	...	99.4	100.4	27.79	27.44
	9	2/ 9/22	1.744	....	....	95	1.110	2.07	1.31	0.95	83.8	48.1	.....	578.4	I	...	99.6	99.6	28.70	28.37
11	3	6/ 3/21	1.191	....	....	75	.....	0.75	0.60	0.96†	38.2	32.0	360.0	339.6	I	...	99.4	98.6	24.47	24.15
	36	7/ 6/21	1.191	38.0	....	54	.....	0.82	0.91	0.96†	57.9	48.7	508.3	515.7	I	...	.....	.....	29.68	28.60
12	7	5/20/21	1.864	....	....	69	0.990	1.44	1.25	0.74	97.7	52.4	.....	638.8	I	...	98.8	.....	28.48	26 93
	19	6/ 1/21	2.055	....	....	67	.....	1.66	1.49	0.96†	94.5	46.0	.....	579.1	I	...	100.0	.....	25.06	24.65
13	48	2/15/21	1.559	40.5	....	76½	0.900	1.70	1.33	0.97	84.1	54.0	623.2	625.7	I	153	100.2	.....	30.54	29.44
14	12	4/11/21	2.070	....	....	65	.....	1.47	1.36	0.96	86.3	41.7	.....	526.1	I	140	99.6	.....	30.09	29.66
15	50	4/ 7/21	2.296	45.5	....	56½	1.230	2.32	2.46	0.96	156.7	68.2	885.3	891.4	I+	153	99.6	100.2	29.89	29.69
16	42	3/30/21	.....	....	....	48	1.239	2.31	2.89	0.95	185.1‡	81.6‡	954.1‡	106.2	II+	185	98.8	99.4	32.10	31.30
17	26	4/ 1/21	.....	....	....	49	.....	2.07	2.53	0.96	161 2‡	83.6‡	989.0‡	104.0	II+	151+	99.4	100.2	30.60	30.24
18	21	3/22/20	1.915	46.1	....	89	.....	2.12	1.43	....	90.9	47.5	.....	539.5	I	...	100.4	98.0	29.19	27.86
		3/23/20	1.895	....	....	61½	.....	1.50	1.46	....	93.1	49.1	.....	607.8	I	...	99.4	96.4	21.33	21.57
		3/24/20	1.875	....	....	67	.....	1.60	1.43	0.96†	91.1	48.6	.....	599.3	I	...	98.6	97.4	27.01	26.72
		3/26/20	2.078	....	....	52½	.....	1.35	1.54	....	98.1	47.2	.....	602.6	I	...	98.8	98.2	23.29	23.13
19	27	12/14/20	1.460	44.5	....	86	.....	1.67	1.17	0.96†	74.1	50.8	.....	575.8	I	...	99.0	101.0	33.86	32.65
	34	12/21/20	1.616	....	....	70½	.....	1.46	1.24	0.96†	79.0	48.9	.....	573.9	I	...	98.8	99.8	31.59	30.22
	50	1/ 6/21	1.914	....	....	45	.....	1.57	2.09	0.96†	133.1	69.6	.....	863.7	I	164	100.1	100.0	31.19	30.20
20	90	1/25/22	2.622	....	....	61	.....	1.89	1.86	0.96†	118.2	45.1	.....	622.1	I	...	98.6	99.2	29.87	29.00
21	10	12/19/21	1.871	....	....	53	.....	1.28	1.45	0.96†	92.2	48.3	.....	607.0	I	122	.....	.....	27.70	27.03

* Where no figures for oxygen are given, the amount measured was less than 1 liter.
‡ Not basal. The infant cried about seven minutes of fifty-minute period.
† Assumed average quotient (see text).

There did not seem to be any relation between the level of the heat production and the prognosis of these infants because some of them gained weight and strength rapidly, and others did not gain at first but did later. In some cases, even with only a slow gain in weight, the heat production increased quite rapidly with age. In Case 11, the heat production increased slowly, 37 calories on the fourth day and 57 on the thirty-sixth day, the weight remaining stationary during this time. The infant died at about 2 months. This single case suggests

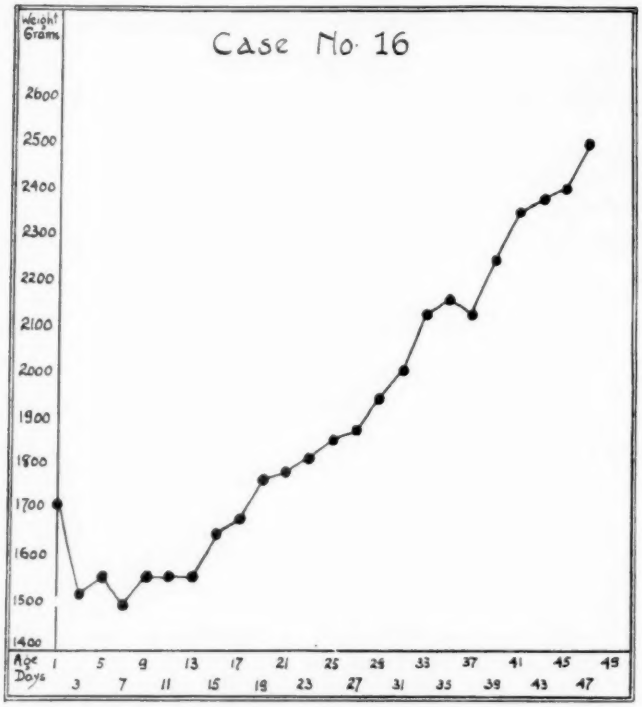

Chart 9.—Weight curve of premature infant.

that a low metabolism which does not increase with age indicates inanition and a poor prognosis. On the other hand, a metabolism that increases with age, as shown by the other cases, does not necessarily mean a good prognosis, because many factors other than the power to produce heat influence the mortality of premature infants. None of the other infants died while being followed by us. The infants in Case 7 died of unknown causes two months after it passed from our supervision.

The relation of the total heat production of premature infants to that of normal infants of the same age is shown in Chart 16, which

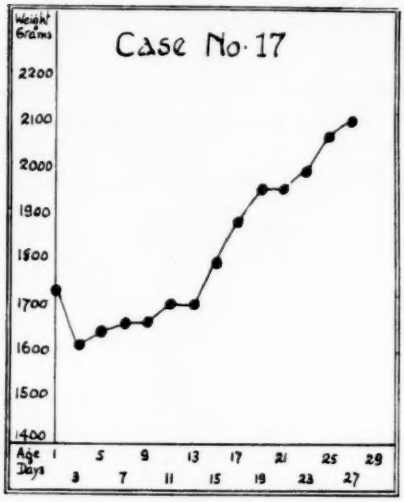

Chart 10.—Weight curve of premature infant.

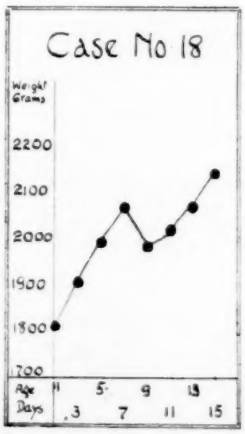

Chart 11.—Weight curve of premature infant.

shows the total heat production for twenty-four hours of normal infants [5] in a solid black line. Below it is the curve for premature infants, indicated by a dotted line. This shows that the total heat production for twenty-four hours of a premature infant is considerably lower and tends to run parallel with that of the normal, full-term infant.

Although the metabolism of premature infants is plotted against their age after birth, it does not represent their physiologic age because

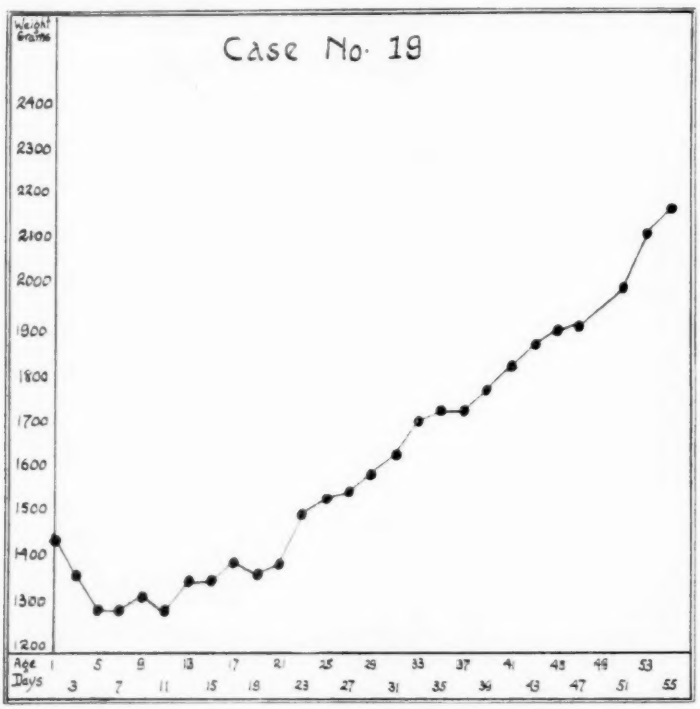

Chart 12.—Weight curve of premature infant.

the expected birth should be 279 days after the last menstrual period. Even this method of reckoning may be inaccurate. The impossibility of obtaining accurate data concerning the age detracts from the value of all the curves in which age plays a part. The question of what is the true age of a premature infant is hard to answer. It can be figured from birth onward, or from the date of the expected birth; in the latter case, the days preceding the expected birth should be indicated as minus days.

The general trend of the metabolism in relation to either the actual birth or the expected birth is lower than, and parallel to, that of normal

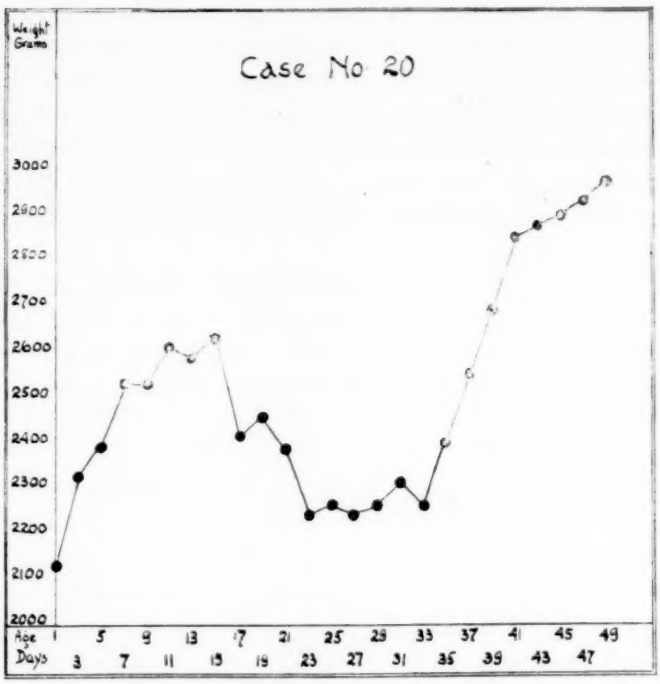

Chart 13.—Weight curve of premature infant.

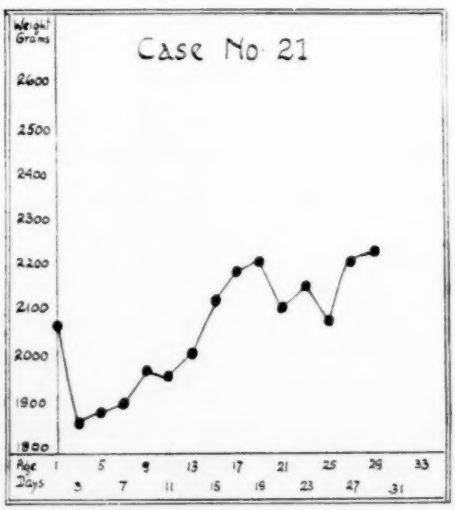

Chart 14.—Weight curve of premature infant.

full-term infants. The curves are closer together when plotted for expected age than for actual age. The very small amount of heat produced by some of these infants is striking. It is consistent with the clinical fact that it is difficult to keep these babies warm, and that constant care and the application of external heat are necessary in order to maintain the body heat. Sudden death in the premature infant during the early days after birth is not at all uncommon, and it would seem that infants with the lowest basal metabolism require the most care to maintain life.

In a few instances, we were able to obtain sufficiently accurate histories to warrant plotting the heat production in relation to the expected

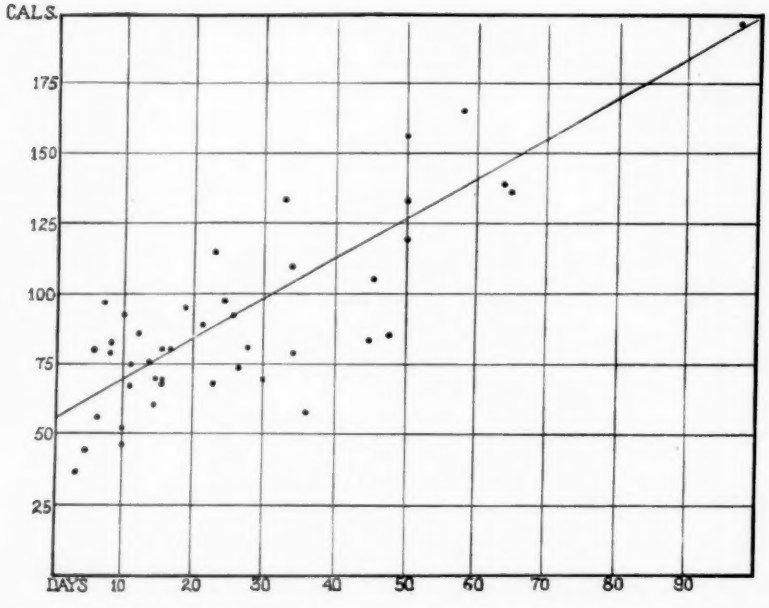

Chart 15.—Basal heat production of premature infants for twenty-four hours, as referred to age.

birth of the infant. This has been done in Chart 17. The days before the expected birth have been indicated as minus days. The general trend of the metabolism is upward, rising with age in a way similar to the curve plotted in Chart 15, which, with Chart 17, shows an increasing heat production with increasing age, whether the days are counted from the actual birth or from the expected birth. The curve of the metabolism of the premature infant is much closer to the normal after the expected birthday than after the actual birthday. The trend in both instances is similar, and shows that, with increasing age and

weight, there is an increase in the total heat production. This apparently means that the premature infant, even in the best surroundings, does not develop as rapidly as it would had it reached full term. It is probable that this handicap persists for several months after birth. An example of a premature infant with malnutrition is to be found in Case J. V.,[9] who had a much lower total metabolism at the age of

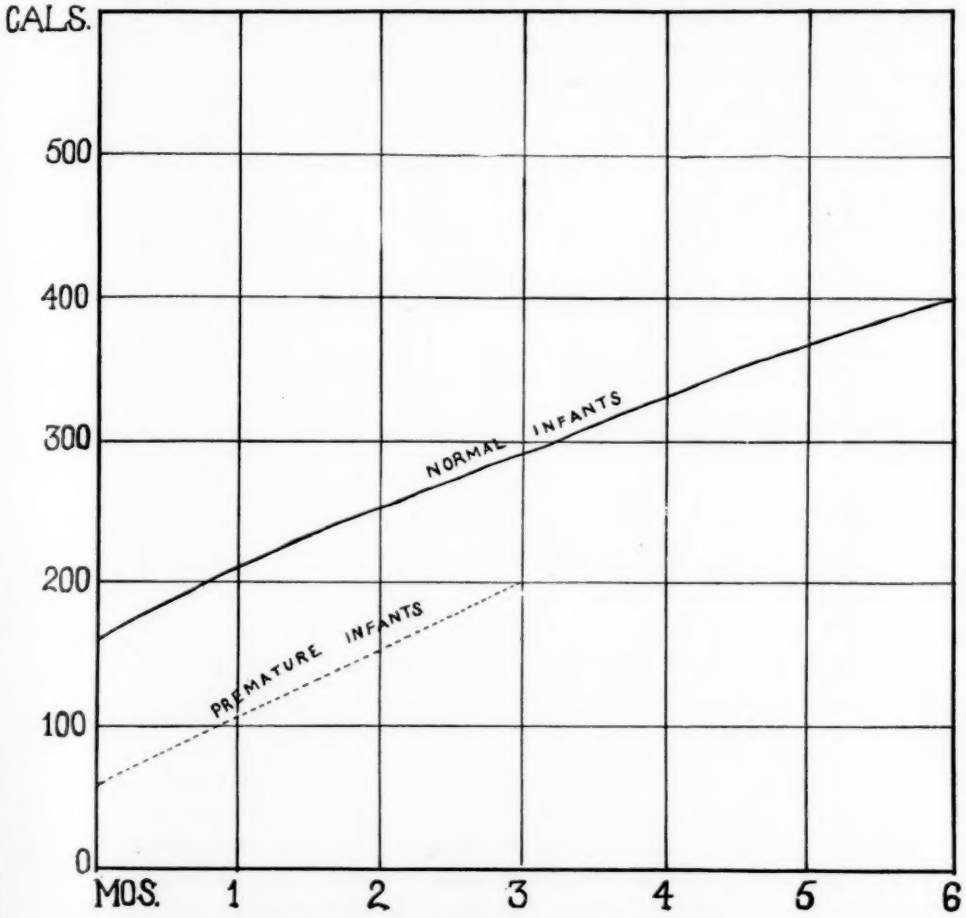

Chart 16.—Total heat production, for twenty-four hours, of normal and premature infants, as referred to age.

8 months than normal infants of the same age. The question still remains to be solved as to how long it takes a prematurely born infant to reach the size and development of the full-term infant. Probably the earliest age at which a 4 or 5 pound (1.81 to 2.27 kg.) premature infant catches up with a normal infant is from 3 to 4 months, and the

smaller the infant, the longer it takes. The relatively greater growth of the premature infant necessitates a larger proportional food intake to supply the material for growth. This, in turn, puts more strain on the organs of digestion and assimilation, which must function normally to obtain successful results.

It has been shown that the total calories produced by normal infants and children, boys especially, can be predicted for a given weight with a considerable degree of accuracy.[11] The heat production of the premature infant has been plotted against body weight in Chart 18, which shows also the curve of the heat production of normal, full-term infants. The heavy babies have a greater heat production than the lighter ones.

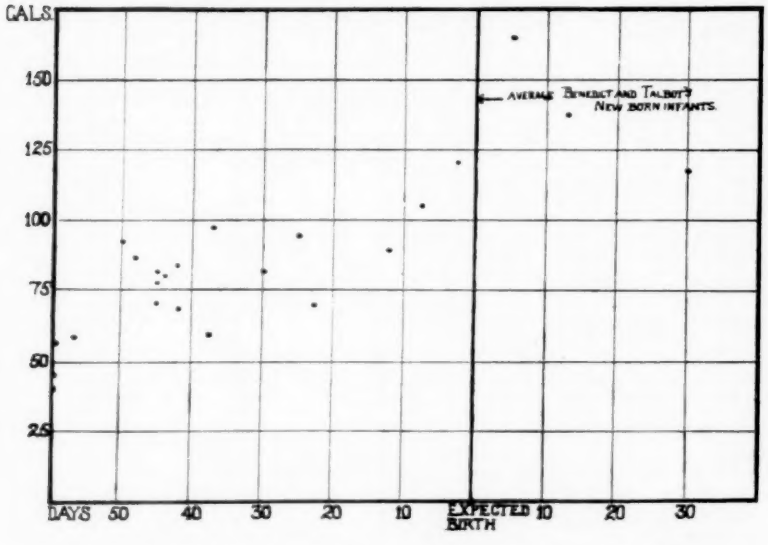

Chart 17.—Total calories in relation to expected birth.

The records of most of the infants weighing more than 1.8 kg. would place them above the curve.[12] Records of the infants weighing between 1.8 and 1.2 kg. would place them in about equal numbers on either side of this line, if it were projected backward. The total heat production plotted against weight appears to be higher in the premature than in the normal infant. This is indicated only in the heavier infants, weighing 2.5 kg. or more, which can be compared with normal infants. This relationship is also found in infants with malnutrition,[13] whether premature or not, and there is good reason to believe that the explana-

11. Benedict: Proc. Nat. Acad. Sc. **6**:9, 1920.

12. Benedict and Talbot: Pub. 302, Carnegie Institute, Washington.

13. Talbot, F. B.: Severe Infantile Malnutrition; Energy Metabolism with Report of a New Series of Cases, Am. J. Dis. Child. **22**:358 (Oct.) 1921.

tion is the same in both instances. The relatively high metabolism of infants with malnutrition is believed to be due to the absence of the diluting factor of inactive tissue, which is represented especially by body fat, and to the presence of a greater proportional amount of active tissue. Whether the lowest portion of the field represents the basal metabolism of late fetal life, and whether projection of the curve backward will predict the metabolism of the fetus from the time of inception to its birth, opens a fascinating field of conjecture.

In plotting the total metabolism against height, the dots fell so widely apart that they did not give a characteristic picture. It was

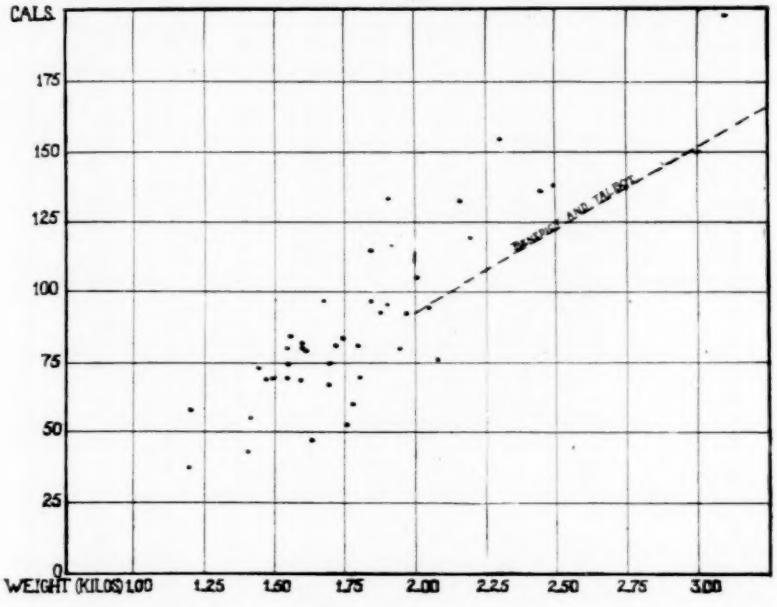

Chart 18.—Basal heat production for twenty-four hours, as referred to body weight.

concluded that, as in the normal infant, the heat production of the premature infant was not proportional to its height.

Recently, considerable interest has been evinced in the relation of the stem length to the caloric needs of children. In a few instances, measurements were taken of the stem length of the infants. This measurement often was made with great difficulty, and there was present a possible error of 1 cm. In Chart 19, the total calories per twenty-four hours are plotted against the stem length. A general increase in the heat production with increasing stem length is shown. The differences are great; for example, there is a difference of 100 per cent. in the heat production of infants with a stem length of 29 cm.

When the metabolism is plotted against the total length of the body, the differences are even greater. It is obvious, therefore, that stem length, in these few observations, does not give a measurement from which to predict the basal metabolism of premature infants, because such prediction can be of real importance only when there is a maximum deviation from the average of 6 per cent. or less.

HEAT PRODUCTION PER KILOGRAM OF BODY WEIGHT

The calories per kilogram plotted against age show distribution very similar to that of normal infants. The most striking feature of this

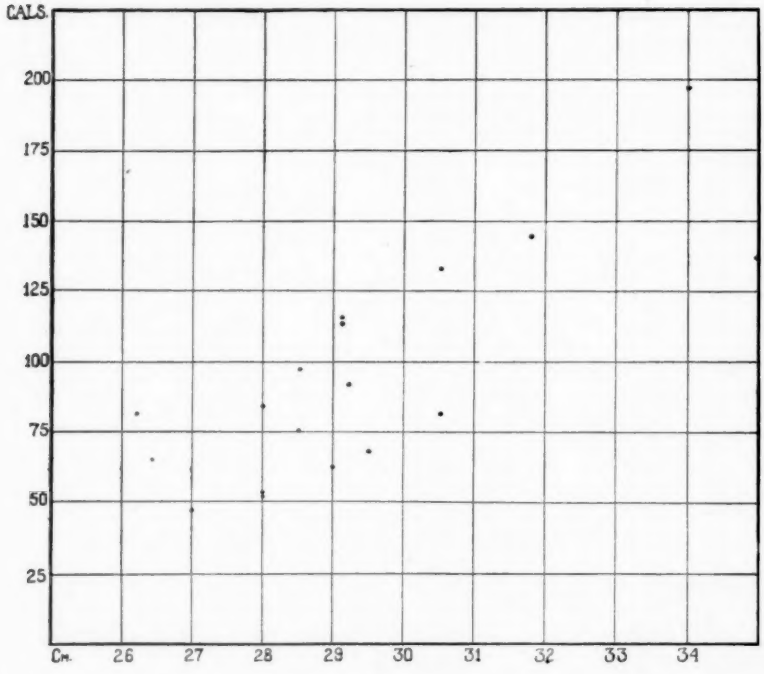

Chart 19.—Total calories, as referred to "sitting height."

picture is that, in the early days of life, the metabolism tends to run much lower than the normal, and after forty days to be higher. Normal infants never have a heat production of less than 41 calories per kilogram, while in eight instances premature infants produced less than this. This seems to indicate that the fire burns very low during the early days of their life; a conclusion quite consistent with clinical experience.

The question arises as to whether the low metabolism is due to the age of the premature infant, or to its small weight. The heat production per kilogram of body weight is of value in showing the influence

of both age and weight (Chart 20 and 21) on the intensity of the metabolism. Since many factors complicate the interpretation of these figures, only general tendencies may be indicated.

The Benedict and Talbot curve for normal infants is plotted in dashes. This shows a general tendency for the heat production of premature infants to be higher than that of normal infants of the same weight (Chart 21).

The heavier the infant, the higher the dots are above the average line of normal infants; the majority of those indicated by dots falling below the line weighed less than 2 kg. This is in accordance with the

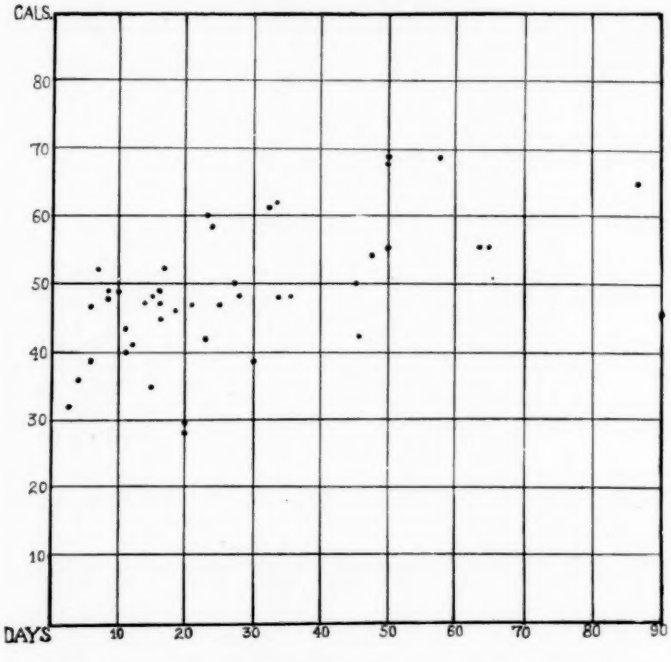

Chart 20.—Calories per kilogram, as referred to age.

variations seen on the age charts. The four lowest dots, although representing the metabolism of very small infants, also represent that of very young infants in the first days of life. Clinically, these infants are very weak and require the greatest attention to maintain their body temperature, so it seems probable that this extremely low metabolism is connected with their age rather than with their weight. This tendency may also be found in the normal new-born infants [8] whose lowest heat production, 32 calories per kilogram, was found on the first day of life, in infants of different weights, respectively 3.3, 3.9 and 4.1 kilograms. It seems probable, therefore, that the metabolism dur-

ing the first days of life, in premature as well as in normal infants, differs from their metabolism after they have become adapted to their surroundings. That the metabolism of the premature should be low longer than that of the normal infant is quite in accord with clinical observations, because the former has to be guarded against the slightest exposure for weeks and the latter only for days.

The tendency of the metabolism of the other premature infants to fall above the average of the normal infant seems to give further evidence to the explanation that their bodies are composed principally of active tissue and are deficient in inactive tissues, such as fat.

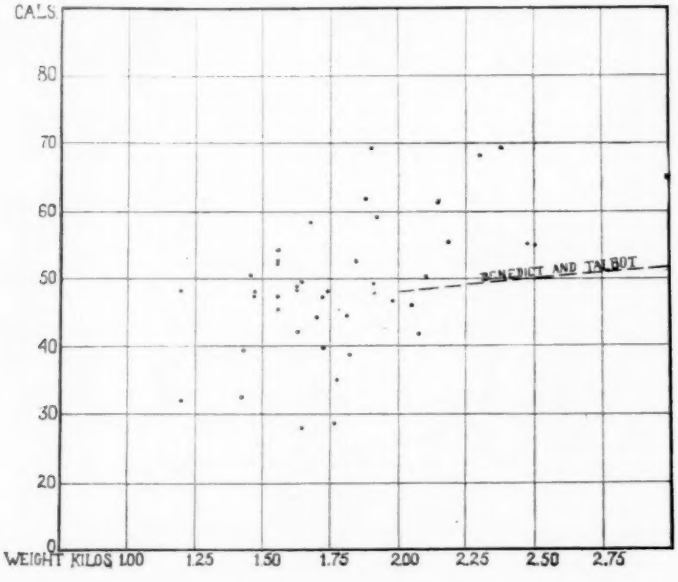

Chart 21.—Calories per kilogram of body weight, as referred to total weight.

HEAT PRODUCTION PER SQUARE METER OF BODY SURFACE

To determine the influence of body surface on the basal metabolism, careful measurements of as many premature infants as possible were taken according to the Du Bois linear measurements. It was found that, with the formula $10.0\sqrt[3]{Wt_2}$ boys and $10.1\sqrt[3]{Wt_2}$ girls recommended by Benedict and Talbot,[12] the surface calculated, by mathematical analysis,[14] approximated more closely the surface obtained by the Du Bois linear formula than by any other method. This factor has consequently been used in Charts 22 and 23, in which the Du Bois

14. Unpublished data.

measurements were not taken both because of the accuracy of the formula and because the results are comparable with other standard curves of normal infants.

These two charts show that with increasing age and with increasing weight, there is an increasing heat production.

Chart 21 shows again the surprisingly low heat production in the early days of life that was indicated in the previous charts. It was first thought by Rubner that the heat production of all animals was 1,000 calories per square meter of body surface. Later, Schlossmann and Murschhauser [15] showed that, in quiet, healthy infants, the heat produc-

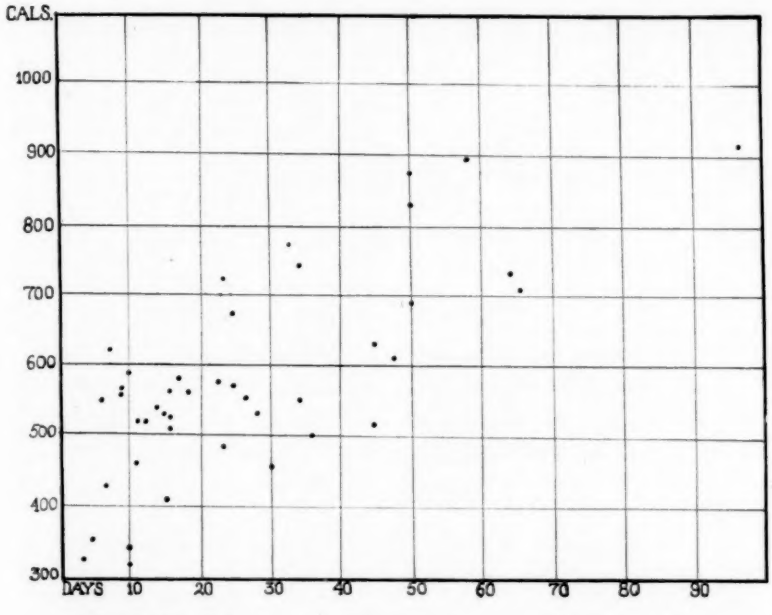

Chart 22.—Calories per square meter, as referred to age.

tion per square meter of body surface might be as low as 866 calories. Benedict and Talbot [8] found that, in new-born infants, it was as low as 612 calories, and that the heat production per unit of surface increased with increasing age up to 18 months. The extraordinarily low findings of 330 and 360 calories in these premature infants are very striking. Hasselbalch's [3] results were likewise low, in one case 366 calories and another 404. These were all in very young infants whose heat regulation was presumably still unstable. The relation between body weight and heat production per unit of surface was not so consistent. The weight of the four infants that had the lowest heat production varied

15. Schlossmann and Murschhauser: Biochem. Ztschr. **14**:369, 1908.

from 1.2 to 1.75 kg.; while the heat production of infants whose weights were between 1.77 and 1.93 kg. varied from 410 to 834 calories. It confirms again the previous charts, which indicate that in very young infants a low metabolism is more often connected with age than with weight. In general, however, the greater the body weight, the higher the heat production. In Chart 23, the Benedict and Talbot curve,[12] plotted in dashes, shows that, in premature infants weighing less than 1.8 kg., there is a tendency for the heat production to be lower than the expected heat production of a normal infant; whereas, in these infants weighing more than 2.1 kg., the heat production was higher than that expected in normal infants.

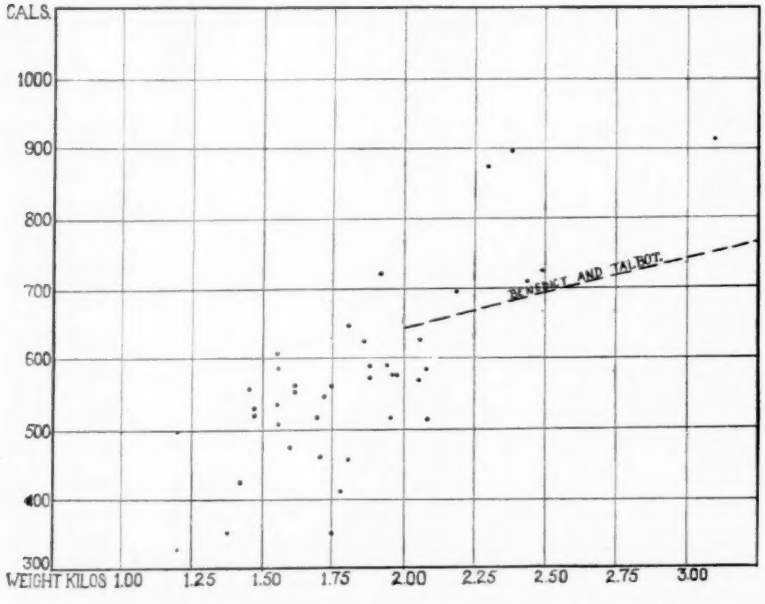

Chart 23.—Calories per square meter, as referred to weight.

The heat production per unit of surface area of the premature infant is, in the majority of instances, less than that of the normal infant. The reason that there is not excessive heat loss in these infants is that the surrounding temperature is kept high enough to prevent this. If a premature infant were exposed to cold, there would presumably result a rapid loss of heat from the body, but not a compensatory increase in heat formation, because it is incapable of forming more heat in early life. As a consequence, the loss of heat from the body is greater than the amount of heat formed, and the body temperature becomes subnormal. If this condition is allowed to continue over any length of time, death nearly always results.

BODY TEMPERATURE AND ITS RELATION TO THE BASAL METABOLISM

The premature infant, especially in the early days and weeks of life, is kept warm with difficulty, and any undue exposure results in a rapid loss of heat from the body, which is not replaced as it is in normal infants by heat formed from muscular exercise. The babies have not enough strength to exercise, and instead of crying or shivering as does the healthy full-term infant, they lie quiet, and extra heat lost from the body is not replaced. In this respect, the premature infant belongs physiologically to the same class as the cold-blooded animal. One would expect, if this were so, that there would be a higher production of heat when the temperature was elevated than when it was low. Case 18, however, did not show any change in the metabolism on each of three successive days when the body temperature varied.

TABLE 6.—*Heat Production of Case 18, with Varying Body Temperature*

Date	Total Calories per 24 Hours	Body Temperature (Fahrenheit)		Temperature of Chamber (Centigrade)	
		Before Period	After Period	Beginning	End
3/22/20	90.9	100.4	98.0	29.19	27.86
3/23/20	93.1	99.4	96.4	21.33	21.57
3/24/20	91.1	98.6	97.4	27.01	26.72

There was no change in the metabolism of any infants in this series that could be attributed to change in the temperature of the body or its surroundings. It seems probable that if the temperature were allowed to remain subnormal for any length of time, the metabolism would also have fallen, just as it does in the coldblooded animal.

THE EFFECT OF EXERCISE ON THE METABOLISM OF PREMATURE INFANTS

It was shown in an earlier publication [8] that, on the average, a maximum increase in metabolism of 65 per cent. may result in the new-born infant from vigorous kicking and crying, and that, up to the age of 6 months, the average increase due to activity may be as high as 40 per cent.

The prematurely born infant is much less vigorous than the infant born at term; the smaller and more premature an infant is, the weaker it is. Cases 16 and 17, given as examples of activity, moved very frequently, but not vigorously, and there was some discussion as to whether their activity should have been recorded as II or III. It was finally recorded as II +, which is a fair estimation when comparison is made with that of normal infants; but when the fact that they were premature infants is taken into consideration, the activities might have been recorded as IV or V. The fact that the activity is relative makes

it difficult to estimate it for a subject that does not conform in other ways with a normal infant. Since the premature infant usually remains very quiet a greater part of the twenty-four hours, what seems to be slight activity is of much greater importance than at any other period of life because it presumably takes more effort to make a slight exertion. Fortunately, it is possible to compare the metabolism of the infant in Case 16 who was moving, with that of her twin sister (Case 15), who was absolutely quiet. This shows that the basal metabolism of the active twin was 11 per cent. higher than that of the quiet twin.

The infant in Case 17 can also be compared with another premature infant of the same weight and approximately the same age.

TABLE 7.—*Comparison of Metabolism of Twin Sisters of Same Weight Showing Effect of Activity*

Case	Weight, Kg.	Total Calories	Metabolism per Kg.	Metabolism per Sq. M.	Pulse	Activity
15 (Malnutrition I)	2.29	156.7	68.0	891	153	I
16 (Malnutrition II)	2.26	185.1	81.6	1,062	185	II+

TABLE 8.—*Comparison of Metabolism of Infants of Same Weight Showing Effect of Activity*

Case	Weight, Kg.	Total Calories	Metabolism per Kg.	Metabolism per Sq. M.	Pulse	Activity
9	1.928	115.4	59.8	737	...	I
17	1.928	161.2	83.6	1.040	151+	II+
22 (16 days)	2.098	185.0	88.2	1,117	...	Crying

The metabolism of the active infant (Case 17) is 40 per cent. higher than that in the basal case (Case 9). Since the recorded activities in Cases 16 and 17 were to all intents and purposes identical, the results show how much more difficult it is to estimate the amount of activity in a premature than in a normal infant. The effect of crying on the metabolism is shown in Case 22, not included in Table 3.

These tables show that muscular activity affects the basal metabolism of the premature as it does the normal infant. The maximum increase of metabolism due to activity found in this series of premature infants was about 40 per cent.

CONCLUSIONS

Determinations of the basal metabolism of premature infants are a contribution to studies of the cycle of life. The heat production is very low when calculated on the basis of total production per twenty-four hours or per unit of body surface. On the basis of the theory as to the relation of heat production to body surface, one would expect the same heat production per unit of surface as in full-term infants; but they

produce less heat, and it is necessary for this reason to give the premature baby much more protection against heat loss in its period of prematurity than at any other period of infancy. The basal metabolism findings are suggestive of what the heat production of the fetus might have been during the last two months prior to birth. The basal metabolism of the premature infant is lower than that of the full-term infant, and remains so for at least three months. Even if the handicap of time is allowed, the premature infant produces less heat on his expected birthday than does the full term infant during the first week of life.

THE TREATMENT OF COLIPYURIA IN CHILDREN*

VALDEMAR POULSEN, M.D., F.R.S.L.
Director of the Children's Hospital Füglebakken
COPENHAGEN, DENMARK

During the thirty years that have elapsed since attention was drawn to the frequent occurrence of colipyuria in childhood, from infancy and onward, research work has been zealously pursued in an effort to find a remedy for this condition. The many methods of treatment suggested and the numerous medicaments introduced—most of them only to disappear quickly—indicate better than anything else how little success has been attained.

In cases in which there is no indication for surgical measures, such as in concrements to be removed or deformities to be corrected, an effort has generally been made to clear up the infection by urinary disinfectants given by mouth and excreted by the kidneys, or the patient is treated with alkalis administered in large doses, in an endeavor to change the reaction of the urine from acid to alkaline, and thereby eliminate the colon bacillus from the urinary duct. The vaccine treatment has been less frequently employed in pediatrics, being reserved mainly for cases in which no other treatment was effective.

Local treatment of the bladder with various antiseptics, usually silver nitrate, has been tried on a larger scale only when the symptoms indicated that the infection had localized there.

In recent years, in my own section of the hospital, I have felt more and more inclined to give preference to local treatment in all cases of colipyuria, regardless of whether they present symptoms of cystitis or of pyelitis. In this I was particularly encouraged after learning of Dr. Arne Johannesen's success with a 2 per cent. solution of silver nitrate, in the children's ward of the State Hospital (Rigshospitalet).

The method I have adopted is, briefly, as follows: Twice a week the patient's bladder is washed out with a solution of silver nitrate, 2 per cent. for the girls and, owing to the pain connected with the treatment, 1 per cent. for the boys. Hexamethylenamin methylencitrate, or phenyl salicylate was often used in addition, in doses according to age. This treatment is continued until the urine is sterile on two examinations at an interval of three or four days, i. e., it shows no growth on agar or broth after incubation for forty-eight hours.

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* Reprint of pamphlet written in honor of Prof. Thorkild Rovsing, April 26, 1922.

In the treatment of colipyuria, I attach great importance to the child's general health, improving it in every possible way. Thus other diseases that the patient may be suffering from, such as dyspepsia and anemia, are treated.

My material, drawn from cases attended in the last two or three years, includes forty-three patients, thirty-four girls and nine boys, all of whom were treated in the manner above described: forty-one at the hospital and two as outpatients.

The accompanying table classifies the patients according to age and sex. The youngest patient was 2 months old, the eldest 11 years.

In every case, the diagnosis was made by examination of the urine microscopically and by culture.

The technical side of the treatment presents no difficulties. In the case of the girls, a small silver catheter is easily introduced into the bladder, and in the case of the boys, a Mercier catheter No. 6, 8 or 10. After the urine has been drawn off, with the catheter, the bladder is washed out with from 10 to 15 c.c. of a lukewarm solution of silver nitrate, 2 per cent., in the case of the girls, 1 per cent. for the boys.

Age and Sex of Author's Patients

Age	Girls	Boys
From 5 months to 1 year	13	8
From 1 year to 5 years	12	
5 years	9	1

In three cases, I have observed hematuria after the treatment, in which apparently the catheter had not injured the patient. The bleeding disappeared during the subsequent twenty-four hours and seemed quite insignificant. Sometimes, there is a rise of temperature after catheterization, but this is of no consequence.

Many children are quiet during the operation; others struggle and scream a great deal, and it cannot be denied that the treatment frightens them and causes them pain, particularly the boys. When children are young and cannot be pacified, we always have a bottle or something else ready for them afterward, to comfort them. For this reason, the treatment is best given in the hospital, where every convenience is at hand and everything thoroughly aseptic. Treatment should never be given in the home unless the mother is willing to cooperate.

By the method described, I succeeded in curing thirty-nine of forty-three patients. All symptoms of the disease disappeared, the urine becoming as clear as water, and free from pus and colon bacilli. The length of time required to render the urine sterile varied in the different cases, the shortest time being noted when cystitis was present, a few treatments of silver nitrate sufficing; whereas, in those cases presenting

symptoms of pyelitis, a longer time was necessary. The average duration of the treatment also varied, being longer for the boys, who were all suffering from pyelitis, than for the girls, many of whom either had or, at an earlier stage of their illness, had had, bladder trouble. The treatment lasted on an average five weeks in cases in which the patient showed symptoms of having or having had cystitis; and eight weeks in other cases. As a rule, the urine soon becomes clear and the pus diminishes in amount and finally disappears. The colon bacillus persists longer; the pyuria becomes a bacteriuria, and it is this condition which ordinarily is slow to improve. Simultaneously with the clearing up of the urine, the patient's other symptoms of disease disappear; the temperature becomes normal; the appetite improves, and the weight increases. A few case histories, illustrative of the prognosis and the course of treatment, are presented herewith.

REPORT OF CASES

CASE 1.—B. F., a girl, aged 8 years, who had been treated six weeks for pyuria twelve months previously at the Municipal Hospital, three days before admission to the Children's Hospital developed abdominal pains, with rise of temperature and frequent and painful urination. On admission, the urine contained pus and traces of albumin, and yielded a growth of *B. coli.* During the first eight days the temperature rose to 102.5 F.

November 26, a 2 per cent. solution of silver nitrate was employed in bladder lavage, and from November 29, 0.5 gm. of phenyl salicylate was added and the mixture employed three times a day, after which irrigation with silver nitrate was employed twice weekly.

December 7, the urine was free from pus but yielded a growth of *B. coli* on culture.

December 16-19, the urine was sterile, and treatment was discontinued.

January 4, the patient was sent home, well.

Control examination, ten months later, revealed that the urine was free from pus and *B. coli.*

CASE 2.—R. N., a girl, aged 9 months, who when younger had been treated at the hospital for rachitis and trismus neonatorum, had been vomiting during the last fortnight. The bowel condition was supposedly normal and there were no symptoms of urinary disorder. The temperature on admission was 104.5 F. The urine contained pus and albumin and yielded a growth of *B. coli.*

May 27, bladder lavage with a solution of silver nitrate, 2 per cent., twice weekly, and with hexamethylenamin methylencitrate, 0.15 gm., three times daily, was prescribed.

June 18, the urine contained only a few pus cells and *B. coli.*

August 9, growths of *B coli.* were obtained.

August 18, growths of *B. coli* (a few colonies) were obtained.

August 23 and 26, the urine was clear; there was no growth, and treatment was discontinued.

There was a steady rise of temperature during the first months, but the temperature became normal during the last months. The general condition improved gradually during treatment, and, September 6, the patient was discharged as cured.

Control examination, three and a half months later, revealed that the urine was free from pus and *B. coli.*

CASE 3.—K. B., a boy, aged 11 years, had complained for about a week of being tired. He had no appetite and had been vomiting. Two days before, hematuria was noted, but there was no lumbar pain, and the urination was neither frequent nor painful. On admission the temperature was 100.8 F. The urine test showed blood; albumin, 4.5 per cent. by Esbach's method; some red and white corpuscles, and casts. The first four weeks, the patient was treated for hemorrhagic nephritis. The temperature remained at 100.4 F. The urine contained less blood and only traces of albumin. Roentgen-ray examination revealed no concrements.

July 16 (four weeks after admission to the hospital), catheterization was performed and showed now that the patient had a colipyuria, for which irrigation with 1 per cent. silver nitrate was employed, twice a week.

August 8, the urine contained a few leukocytes and *B. coli*, with traces of albumin and blood.

August 13 and 16, the urine was sterile. Treatment was discontinued. The temperature was normal from August 10 on, and the patient was discharged, August 24, as cured.

Control examination, fourteen months later, revealed that the urine was free from pus and *B. coli*.

CASE 4.—L. P., a boy, aged 11 months, became ill a month previously, with rise of temperature and chills. Three or four days thereafter, the physician made a diagnosis of pyuria, and treated the patient with medicine and boiled water. As there was no improvement, the child was admitted to the hospital. The temperature was 101 F. The urine contained quantities of leukocytes and *B. coli*.

November 25, orders were given for irrigation with 1 per cent. silver nitrate, twice weekly.

December 14, the urine contained a few leukocytes and *B. coli*.

December 20, hexamethylenamin methylencitrate, 0.25 gm., three times daily; was prescribed.

January 4, 7 and 12, the urine was clear and sterile. Treatment was discontinued. The temperature on a few occasions was about 100.4 F., and had been normal since December 25. The patient was discharged, January 14, as cured.

Control examination, ten months later, revealed that the patient had been well since discharge. The urine was clear, and free from pus and *B. coli*. (no growth on agar and broth after forty-eight hours).

The results in all the thirty-nine cases were, with but slight variation, similar to those of these four cases, the patient being discharged with sterile urine, apparently cured.

Besides these thirty-nine patients, I have treated four, of whom two were discharged with colipyuria and two with bacteriuria. Below is a report of these cases.

CASE 5.—H. R., girl, aged 5 years, during the previous week had complained of abdominal pains, and had sometimes screamed with pain during the night. The temperature was 101 F., and there was painful urination. The temperature on admission was 100.8 F. A urine test revealed traces of albumin, numerous leukocytes and *B. coli*.

March 20, irrigation of the bladder with 2 per cent. silver nitrate, twice a week, was prescribed, and phenyl salicylate, 0.3 gm., four times daily, as well as 1 pint of boiled water daily.

April 3, roentgen-ray examination revealed no signs of calculi.

April 7, phenyl salicylate was discontinued. Hexamethylenamin methylencitrate, 0.35 gm., was employed, three times a day.

April 19, the urine contained a few leukocytes and *B. coli.*

May 4 and 11, the urine was sterile, and treatment was discontinued.

May 15, the patient was discharged as cured and sent into the country.

Three months later, she was again admitted. Four days previously, after returning from the country, she had had a rise of temperature to 102.2 F., with frequent urination. The urine contained pus and *B. coli.*

August 20, irrigation of the bladder was prescribed with 2 per cent. silver nitrate, twice a week, and phenyl salicylate, 0.5 gm., three times a day.

September 3, phenyl salicylate was discontinued.

September 4, the urine contained pus and *B. coli.*

September 5, irrigation with silver nitrate was continued, with autogenous vaccine treatment.

October 7, the urine still contained pus, though less, and *B. coli.* Treatment with silver nitrate and vaccine was discontinued. Phenyl salicylate, 0.5 gm., three times a day, was again prescribed, but this treatment seemed of benefit for only a week.

October 31, the urine still contained pus and *B. coli.* The patient was discharged, November 2.

Control examination, two years later, revealed that the urine did not contain pus, but yielded a growth of *B. coli.* The patient suffered from enuresis.

CASE 6.—U. P., a girl, aged 9 years, who two years previously had suffered from nephritis, had been confied to bed during the previous week, complaining of lumbar pains. On admission to the hospital, the temperature was 100.4 F. The urine contained fetid pus, traces of albumin, and *B. coli.*

October 19, irrigation with 2 per cent. silver nitrate, twice a week, and phenyl salicylate, 0.5 gm., three times a day, was prescribed.

November 9, the urine contained numerous leukocytes, but yielded no growths of *B. coli.*

November 14, a growth of *B. coli* was obtained.

November 25, phenyl salicylate was discontinued, and hexamethylenamin methylencitrate, 0.3 gm., three times a day, was prescribed.

November 29, no growth of *B. coli* was yielded; thereafter, there was sometimes a growth of *B. coli,* sometimes none.

December 6, numerous leukocytes were noted.

December 29, the patient was discharged. The general health was good; there was an increase in weight of 5.5 kg., but the urine still contained pus and *B. coli.* The patient was not subjected to roentgen-ray examination. Control examination was refused.

CASE 7.—L. J., aged 5 months, two days previously in the evening, was suddenly seized with cramp. Since then, there had been four attacks. When the patient was admitted, the temperature was 100.4 F.; in the evening, 104 F. The urine contained pus, no albumin and *B. coli.*

May 12, irrigation with 1 per cent. silver nitrate, twice a week, was prescribed and hexamethylenamin methylencitrate, 0.1 gm., three times a day.

May 20, dilation of the phimosis was done.

May 29, the urine was clear and free from pus, but yielded *B. coli.*

June 19, the urine contained no pus, but was still positive for coli.

June 25, the urine continued to yield *B. coli.* Irrigation with silver nitrate was discontinued.

June 28, treatment with hexamethylenamin methylencitrate, 0.15 gm., three times a day, was continued.

July 15, the urine contained *B. coli.*

July 18, the urine contained numerous leukocytes and *B. coli.*

July 25, hexamethylenamin methylencitrate was discontinued, and sodium bicarbonate, 0.25 gm., four times a day, was prescribed. From August 11, sodium bicarbonate, 0.25 gm., was employed, six times a day.

August 17, the urine contained pus; the bowels were loose, and sodium bicarbonate was discontinued.

September 2, the urine contained *B. coli,* but no leukocytes.

September 11, hexamethylenamin methylencitrate, 0.3 gm., three times a day, was prescribed. The patient was discharged, September 12, treatment with hexamethylenamin methylencitrate and 1 per cent. silver nitrate to be continued at home, once a month.

October 16, the urine was free from pus and *B. coli* (no growth on agar and broth after forty-eight hours). Treatment was discontinued.

Control examination, one month later, revealed that the urine was free from pus and *B. coli.*

In addition to colipyuria, the patient suffered from chronic dyspepsia during her entire stay in the hospital. This condition was cured by the time she was discharged. During the first months, there was a steady rise in temperature, but the temperature was normal during the latter months.

CASE 8.—H. J., a boy, aged 5 months, who had had a rise of temperature for a week while at home, and a temperature of 101.8 F. on admission to the hospital, had pus and *B. coli* in the urine. He also suffered from chronic dyspepsia.

November 20, irrigation of the bladder with 1 per cent. silver nitrate, twice a week, was prescribed, and phenyl salicylate, 0.1 gm., three times a day.

December 7, the urine contained pus and *B. coli.*

January 1, the urine was clear but yielded a growth of *B. coli.*

January 10, the urine contained some leukocytes and *B. coli.*

February 2, the urine yielded a growth of *B. coli.*

February 21, phenyl salicylate was discontinued and hexamethylenamin methylencitrate, 0.2 gm., four times a day, prescribed.

March 18, the urine contained pus and *B. coli.*

April 4, the urine yielded pus in diminished quantities, and a growth of *B. coli.* Silver nitrate was discontinued, hexamethylenamin methylencitrate continued.

May 3, the urine was clear but yielded a growth of *B. coli.*

May 6, the patient, who was now cured of a chronic dyspepsia and whose temperature during the first months had only risen now and then, was discharged, but the treatment with hexamethylenamin methylencitrate, 0.2 gm., four times a day, and 1 per cent. of silver nitrate was to be continued at home, once a month.

November 18, the urine was free from pus and *B. coli.*

Control examination, one month later, revealed that the general condition was good. The urine was free from pus, and free from growth of *B. coli.*

COMMENT

Neither of the last two patients was examined by roentgen ray. I can give no satisfactory explanation as to why the treatment failed in these four cases. The history of these cases is similar to that of many in which the result was satisfactory. In three cases, I should, from my present experience, have continued the silver nitrate treatment considerably longer, and possibly it would have been successful. The fourth patient (Case 8) was so energetically treated with silver nitrate, during three and a half months, that prolonging treatment further could scarcely be presumed to be of any value.

If a comparison is made between my cures—thirty-nine patients cured, or at least temporarily cured, out of forty-three treated—and the results attained by others, it will be seen that their percentage of cures

is not so high. At any rate, I have not seen any; not if the urine must be free from pus and sterile on two consecutive examinations, before a case of colipyuria can be pronounced cured. In this connection, I would mention some figures from Denmark [1] and from Norway.[2]

Meyer's principal treatment was as follows: "To give as much fluid as possible, boiled water and hexamethylentetramin, from 0.15 to 0.5 gm., three times a day, in some cases showing a certainty or possibility of cystitis." He employed irrigation of the bladder with a solution of 2 per cent. silver nitrate; in others, with alkaline urine, a mixture of boric acid was used, and in seven cases, *B. coli* vaccine. In a few cases, the patients were either not treated at all or were treated only with water by mouth. Meyer gives a record of sixty-eight cases, four of the patients dying from bladder conditions, while five died from other causes. Meyer believes that pyuria did not play any direct part in the cause of death. Thirty of the patients were discharged as cured, or, as Meyer cautiously adds, apparently cured, since, in the beginning, he draws his conclusions as to cure only from the fact that the urine was free from pus, without bacteriologic examination, and so does not know whether the urine in all the thirty patients was sterile when they were discharged. Nineteen were discharged with pyuria, nine with bacteriuria and one with nephritis.

Collet reports more than 100 cases, treated in various ways, fifty-three with urinary antiseptics alone, twenty with antiseptics and other treatment; fourteen with irrigation of the bladder, twelve of whom were treated with urinary antiseptics also or alkaline preparations; four with vaccine, in three of whom this was combined with other treatment, and eight alternately with alkaline preparations and other treatment.

Fifty-two of these 100 patients of Collet's were discharged as clinically cured, "with clear urine. Of these, eighteen had sterile urine, forty had pyuria or bacteriuria when discharged, and eight died."

Meyer mentions the case of a 3 year old child suffering with pyuria who was cured by silver nitrate but had a relapse, although she was discharged with sterile urine. This was also true of H. R. (Case 5), who was discharged after the urine had been examined twice, both times with negative results, but was admitted again, three months later, with a recidivation. I have noticed several times that the urine may for a long time give alternately a negative and a positive culture. Taught by these experiences, I hesitated to regard my thirty-nine patients as permanently cured. I, therefore, endeavored to secure a control examination later on. Of the thirty-nine patients, thirty were

1. Meyer, Adolf: Experiences with Pyuria in Children, 1907
2. Collet, Arthur: Urinary Infection in Childhood, 1919.

examined. One had died of bronchopneumonia, and eight did not come for examination.

Of the thirty patients examined, twenty-one had sterile urine. The time elapsing between discharge from the hospital and the control examination was in two cases one month, in one case, three months, and in three cases, between three and six months. In six cases, between six and twelve months had elapsed; while in the case of nine patients, more than one year had elapsed. It may, therefore, presumably be said of these patients that they are cured.

In the nine patients suffering from bacteriuria, the urine was as clear as water and free from pus but yielded a growth of *B. coli.* All of these patients were girls, six under 12 months, two between 1 year and 2 years, and one, 5 years old. Two had cystitis while in the hospital; seven, pyelitis. All patients but one who had cystitis were treated with hexamethylenamin methylencitrate in addition to silver nitrate. One of these patients had sterile urine at three different times before being discharged, the others (eight), twice. The course of the disease in these cases did not apparently differ from that of the twenty-one patients with sterile urine. Only two of these were examined by roentgen ray, and showed no calculi.

Four of the above mentioned patients were again treated with silver nitrate, two with hexamethylenamin methylencitrate in addition, and two without. All had sterile urine after one or two treatments. Three have not yet had a control examination. The fourth had a sterile urine, a month later.

Unfortunately, Meyer has not made a control examination of his thirty patients apparently cured. Collet writes that, of his eighteen patients with sterile urine, one at the control examination had bacteriuria; one has not been heard from, and sixteen had sterile urine.

By means of the control examination, it has been proved that children suffering from colipyuria cannot be said to be finally cured even if by this treatment the urine is proved sterile by two or three consecutive tests. It is necessary to follow the case after the treatment is stopped and to test the urine bacteriologically. The thirty-nine cases cured by me may, therefore, be reduced somewhat, how much it is impossible to say definitely, as the figures are so small that chance may play a part in the calculation. However, I believe that I am not far wrong in putting the percentage of patients cured at 66, when I take into account the twenty-nine patients who returned for the control examination, about two thirds of whom were finally cured.

As will be seen by the introductory remarks concerning my method of treatment, in all cases irrigation was performed twice a week, with a 1 or 2 per cent. solution of silver nitrate. In most cases hexa-

methylenamin methylencitrate or phenyl salicylate was employed alternately. One patient was given alkalis for a short time, and a few, *B. coli* vaccine. All the younger patients were given plenty of water and their food was principally liquids. The older ones had fruit syrup and water between meals. Their general health was given careful attention, and complications were energetically treated.

When so many methods of treatment are combined, and when, in addition, a disease follows so whimsical a course, and is not infrequently cured spontaneously, it is difficult to say definitely which is the principal factor in the result achieved. I have not the slightest doubt that it was attained by a consistent treatment with silver nitrate, or why should my results be so much better than those of others? On the other hand, it may be possible that the contemporary treatment with hexamethylenamin methylencitrate or phenyl salicylate has also contributed to the results, even if this cannot be proved.

To every one here in Denmark, where we are well acquainted with the significance of irrigation with silver nitrate as a urinary disinfectant, it is not surprising that the treatment with silver nitrate was effective when cystitis was present; but it is surprising to see a therapeutic effect attained in cases suspected to be pyelitis. I can give no reasonable explanation as regards this, unless, in far more cases than is generally believed, the infection is one of the bladder, the focus of infection being there.

I do not quite agree with the authors who consider the administration of silver nitrate to children suffering from pyuria useless, even injurious. And when the treatment has not given desirable results elsewhere, except in cases in which cystitis was present, I believe this to be entirely due to the fact that treatment was not carried out consistently and a too weak solution was administered.

THE EFFECT OF DRUGS ON BLOOD AGGLUTININS*

DAVID M. SIPERSTEIN, M.D.
AND
ANNA L. KVENBERG
MINNEAPOLIS

Although the status of blood grouping and its value in preventing harmful reactions have been definitely established, more or less severe reactions following blood transfusions are still reported in the literature. Attempts have been made by many men to explain the phenomena observed. Unger [1] has urged the advisability of grouping the donor's blood directly against the blood of the recipient. Lately, several cases have been reported which demonstrate that our previous conceptions of hemolysis and agglutination may need some revision. Astrowe [2] has pointed out the necessity of repeated tests of donor's versus recipient's blood before each transfusion. West,[3] in a later note, cites a case in which hemolysis of the donor's cells took place without preliminary agglutination.

In January, 1922, Eden [4] advanced the theory that the agglutinins present in the blood could be changed or altered in various degrees. This change from one group to another is apparently not permanent, but persists for some appreciable time. He states that it can be obtained by the administration of various drugs; by chloroform-ether anesthesia, or by prolonged exposure to the roentgen rays (Table 1).

Later, Levine and Segall [5] reported that prolonged etherization causes a temporary change in the iso-agglutinative phenomena, thereby confirming Eden's results.

Recently, Huck and Peyton [6] reported twenty-five cases in which patients were subjected to ether anesthesia without any change in the blood groups.

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* Received for publication, May 5, 1923.

* From the Minneapolis General Hospital.

1. Unger, L. J.: Therapeutic Aspect of Blood Transfusion, J. A. M. A. **73**:815 (Sept. 13) 1919.

2. Astrowe, P. S.: Hemolysis Following Transfusion, J. A. M. A. **79**:1511-1514 (Oct. 28) 1922.

3. West, P. C.: Hemolysis Following Transfusion, J. A. M. A. **79**:1950 (Dec. 2) 1922.

4. Eden, Rudolf: Die Bedeutung der gruppenweisen Hamagglutination für die Agglutinationsgruppen durch Medikamente, Narkose, Röntgenbestrahlung. Deutsch. med. Wchnschr. **48**:85-87 (Jan. 19) 1922.

5. Levine, E. C., and Segall, H. N.: Posttransfusion Reactions; Alterations in Blood After Ether Anesthesia and After Blood Transfusion, Surg., Gynec. & Obst. **35**:313 (Sept.) 1922.

6. Huck, John C., and Peyton, Sarah M.: Study of Iso-Agglutinins Before and After Ether Anesthesia, J. A. M. A. **80**:670-671 (March 10) 1923.

Owing to the manifest importance of the question involved, we repeated Eden's original experiments on a series of patients. Data and results obtained are given in Table 2. The observations were made on children in our pediatric service, varying in age from 3 to 12 years. The patients were grouped before and at irregular intervals following the administration of the medication desired. The Lee method and Moss classification for blood grouping were used throughout the present study.

TABLE 1.—*Tabulation of Results Obtained by Eden (1922)*

Case	Original Blood Group	Drug Employed	Amount	Result	Remarks
1	III	Quinin	1 gm. for 2 days	Changed to Group I	Nine days later in Group III
2	II*	Quinin	5 gm., 1st day; 1 gm. 2d day	Group I	
3	III	Calcium lactate	0.4 gm.	Group I	
4	III	Calcium lactate	1st day, 0.2 gm.; 2d day, 0.2 gm.; 3d day, 0.2 gm.	Group I	Group III on fourth day
5	IV	Antipyrin	0.5 for 18 days	Group I	Fifteen days later in Group IV
6	IV	Solution of potassium arsenite (Fowler's solution)	2 drops 3 times a day to 8 drops 3 times a day and back; 3 drops 3 times a day (12 days)	Group II	Remained in Group II for 19 days; 23 days later, in Group III; 33 days later, in Group IV
7	IV	Chloroform-ether	.....	Group III	Four days later in Group IV
8	IV	Chloroform-ether	30 min.	Group III	
9	II	Chloroform-ether	30 min.	Group IV	Three days later in Group II

* In three other patients, belonging to Group II, after exposure to the roentgen ray for long periods of time (from three to twelve hours), the grouping changed to I in one case and to IV in the two other cases.

RESULTS

It is at once apparent that our results are entirely negative. Drugs given to their therapeutic limits failed to produce any change in the iso-agglutinative phenomena. In one case (Case 11, Table 2) a patient in Group III, with a total blood volume of approximately 1,000 c.c., received 700 c.c. of Group IV blood intravenously without any change in blood group.

Von Dungern and Hirschfeld [7] believe that only two different agglutinins exist in human serum and that both are present in Group IV serum. Unger [1] has proved this in an ingenious way. Employing Group IV serum, he was able, after taking out the agglutinins for Group II cells, to obtain agglutination of Group III cells.

TABLE 2.—*Results of Application of Eden's Experiments to Authors' Series*

Case	Medication		Original Group	End-Result	Remarks
	Drug	Amount			
1	Quinin sulphate	15 grains (1 gm.)	IV	IV	
2	Quinin sulphate	15 grains (1 gm.)	III	III	
3	Quinin sulphate	15 grains (1 gm.)	IV	IV	
4	Quinin sulphate	10 grains (0.6 gm.)	IV	IV	
5	Quinin sulphate	15 grains (1 gm.)	II	II	
6	Quinin sulphate	40 grains (2.6 gm.)	IV	IV	Toxic symptoms
7	Calcium lactate	10 grains (0.6 gm.)	III	III	
8	Calcium lactate	10 grains (0.6 gm.)	II	II	
9	Calcium lactate	10 grains (0.6 gm.)	II	II	
10	Calcium lactate	10 grains (0.6 gm.)	IV	IV	
11	Transfusion	700 c.c.	III	III	Purpura hemorrhagica; received Group IV blood
12	Transfusion	150 c.c.	IV	IV	
13	Ether (anesthesia)*	.....	III	III	
14	Ether (anesthesia)	.....	III	III	
15	Ether (anesthesia)	.....	II	II	
16	Ether (anesthesia)	.....	II	II	
17	Ether (anesthesia)	.....	II	II	
18	Ether (anesthesia)	.....	IV	IV	
19	Ether (anesthesia)	.....	II	II	
20	Ether (anesthesia)	.....	IV	IV	
21	Ether (anesthesia)	.....	II	II	
22	Ether (anesthesia)	.....	II	II	
23	Ether (anesthesia)	.....	II	II	
24	Ether (anesthesia)	.....	II	II	
25	Solution of potassium arsenite (Fowler's solution)	1 to 10 minims, three times a day, and down	II	II	
26	Solution of potassium arsenite (Fowler's solution)	1 to 10 minims, three times a day, and down	II	II	

* Average time of administration of anesthetic was thirty minutes in each case.

The results Eden obtained would tend to show that certain drugs have the property of removing one agglutinin or both agglutinins from

7. Von Dungern and Hirschfeld, L.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **4**:284, 1910.

the serum. It seems inconceivable, however, that an agent which apparently removes an agglutinin in one case should add an agglutinin in another case (Cases 9, 11 and 12, Table 2).

Our experiments show that the cause of reactions following blood transfusions cannot be laid apparently to any external agent. The reason may be looked for along the lines suggested by Unger and Dyke.[8]

CONCLUSION

Serum agglutinins are apparently not altered by ether anesthesia, blood transfusion or the drugs employed in the present study.

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8. Dyke, S. C.: On Isohemagglutination, Brit. J. Exper. Path. **3**:146 (June) 1922.

A MIXED TUMOR OF THE CERVIX AND VAGINA IN AN INFANT*

STAFFORD McLEAN, M.D., AND MARTHA WOLLSTEIN, M.D.
NEW YORK

Mixed tumors of mesodermal origin, polypoid in form, often termed grapelike sarcomas, and malignant in character, are found in the vagina and also in the uterine cervix of young children. They occur more frequently in the vagina; for, while only four undoubted cases of primary mixed tumors of the cervix in young subjects have been reported, there are records of sixteen cases of primary mixed neoplasms of the vagina in children from 6 months (Hauser[1]) to 7 years (Demme[2]) of age. In addition, there are two cases in the literature in which both cervix and vagina were involved in the growth; and, although it is asserted that the cervix was the original seat of the tumor, the description of the organs at necropsy makes it impossible to substantiate this claim. The case herein reported, then, becomes the third in which the cervix was the probable seat of the primary growth, although, in view of the extensive involvement of the vagina, it was impossible to fix the point of origin.

REPORT OF CASE

History.—J. H., aged 10 months, born in the United States, of American parentage, admitted to the Babies' Hospital, April 13, 1920, was under observation sixty-nine days. The chief complaint was pallor and bloody discharge on the diaper, observed for two months. The father and mother were healthy. There had been but one pregnancy. The birth weight was recorded as 8 pounds (3,630 gm.).

The child was born at term, with normal delivery. She was nursed six months, and then a milk, water and cane sugar mixture was substituted on account of failure of the mother's milk. Some further changes made in the character of the feeding were of little importance.

Three months prior to admission, it had been noted by the mother that the stools occasionally contained mucus, and two months previously an occasional streak of blood in the stool was first noted. Some times clots of blood were observed on the napkin. The mother thought that the presence of blood on the napkins was regularly associated with the passing of urine or feces. Not infrequently, mucus and blood were noted on the same napkin. Blood was noted also on the vulva, but never in the anal folds. During this period of two months, the bloody discharge had not been constantly present, somtimes two weeks elapsing without its appearance.

The child had from four to five stools daily and urination was frequent.

Physical Examination.—The general appearance of the child was that of a well-nourished, well-developed infant, with marked pallor but not acutely ill. The admission weight was 13 pounds and 3 ounces (about 5,980 gm.). One lower incisor tooth was present. The lungs and heart were apparently normal;

* Received for publication, May 5, 1923.

* From the Babies' Hospital of the City of New York.

the abdomen was normal in contour, and the spleen and liver were not palpable. There was no enlargement of the superficial lymph nodes.

When the labia were separated, a small amount of fresh blood was discharged, and subsequently, during a proctoscopic examination, considerable blood of very foul odor escaped from the vagina. The mucous membrane of the intestine seen through the proctoscope was normal in character, and no blood followed withdrawal of the instrument. Other physical findings were negative.

The erythrocytes numbered 2,800,000; the hemoglobin was 65 per cent.; the leukocytes numbered 14,800: polymorphonuclears, 60 per cent.; lymphocytes, 40 per cent.

The child was examined by several physicians and surgeons, and on both rectal and vaginal examination, a small, firm, bleeding mass of irregular contour, about the size of an egg, was palpated in the cervix of the uterus, extending into the vagina. The mass extended more to the left than to the right and seemed to lie close to the rectal wall, but there was no communication between the rectum and the vagina. Curettage was performed, and the material removed was examined microscopically, with the result that a diagnosis of angiosarcoma was made.

Course and Treatment.—During the period of observation in the hospital, there was progressive loss of weight, the lowest, 9 pounds and 4 ounces (about 4,200 gm.), being recorded the day the child died.

The surgeons were of the opinion that the disease had advanced beyond the stage where surgery might be of benefit. At their suggestion, radium treatment was administered (by Dr. Harold C. Bailey). The first exposure of 3 hours of 100 millicuries of filtered radium to the neck of the uterus was given fifteen days after admission. There was no bleeding from the vagina for six days thereafter, although oozing of blood had been constantly present previous to the radium treatment. After the period of 6 days it recurred, continuing at intervals until death. Three weeks from the date of admission, 1,863 millicuries of filtered radium was applied 10 cm. distance from the symphysis for three and one half hours, with a total dosage of 6,055 millicurie hours.

A slight erythema of the skin was noted after this application, and in the evening there was a rise in temperature.

One month after admission a third radium exposure of 100 millicuries was given for 300 millicurie hours. The radium was placed in the uterus with a silver wire applicator giving 0.6 mm. filter. There was no rise in temperature following this application.

Six weeks from the date of admission, the record shows that there was a fairly large conical mass felt well down in the abdomen. This mass was apparently pressing against the sacrum and coccyx. It resembled in shape an adult uterus.

The temperature was slightly elevated during the entire period of observation, with frequent rises to almost 103 F. At one time, the temperature rose above 103 F., but this was probably due to a complicating otitis. Frequent blood examinations showed a secondary anemia, varying in severity. The highest red cell count was 4,000,000, and the lowest, 1,800,000. The hemoglobin varied from 40 to 75 per cent. The highest leukocyte count recorded was 14,800; the lowest, 8,000.

A transfusion of 200 c.c. of blood by the direct method was given ten days after admission. The blood count prior to the transfusion showed 2,800,000 erythrocytes; 65 per cent. hemoglobin; 14,800 leukocytes; 60 per cent. polymorphonuclears, and 40 per cent lymphocytes.

A second blood count immediately following the transfusion showed that the erythrocytes had increased to 4,000,000 and the hemoglobin to 75 per cent.

During the child's stay in the hospital, the pallor became progressively more marked. The anorexia became aggravated, desquamation of the skin cover-

ing the abdomen occurred and trophic ulcers made their appearance on the right side of the head, two days before death, which occurred sixty-nine days after admission to the hospital.

Necropsy.—The body was that of a poorly developed and poorly nourished infant.

Lungs: There was an old fibrinopurulent pleurisy between the lobes of the right lung, with inspissated, yellowish exudate. Many subpleural, capillary hemorrhages were present over both lungs, and there was some emphysema anteriorly. The upper portion of the right lower lobe contained a small abscess, 1 by 1 cm. in diameter.

Trachea and Bronchi: These were normal. The bronchial lymph nodes were not enlarged.

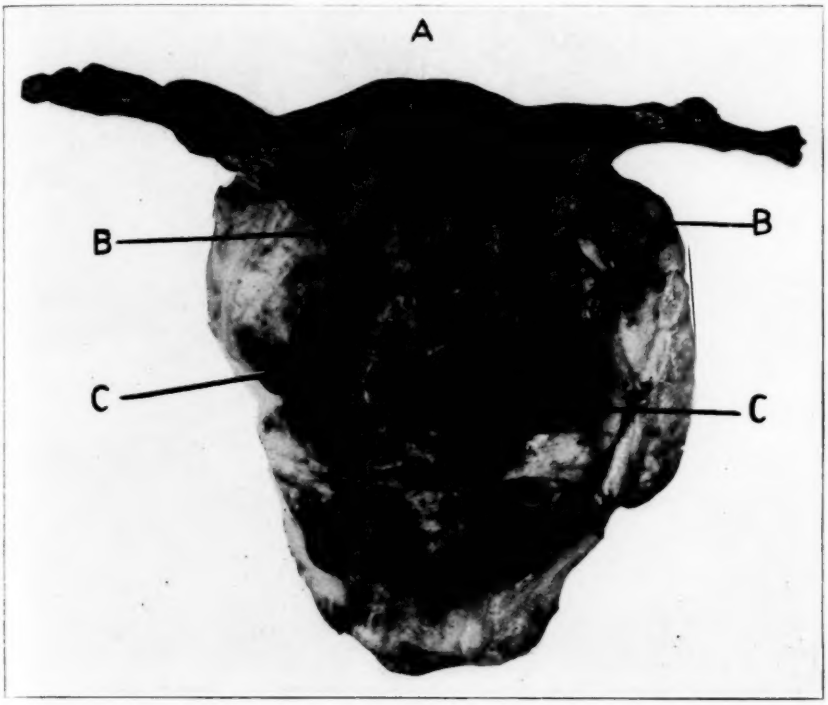

Fig. 1.—*a,* body of uterus with line of congestion on the mucosa; *b,* neck of uterus, both lips involved in the neoplasm; *c,* new growth involving the anterior wall of the vagina more than the posterior wall.

Heart: This was normal. The foramen ovale was closed.

Thymus: This was normal.

Liver: The organ was not enlarged; it was moderately fatty. Some small subcapsular hemorrhages were present on the upper surface. No metastatic nodules were present.

Spleen: Measurements were 3 by 7 cm. The organ was normal in consistency, and contained no metastatic nodules.

Stomach: There were many capillary hemorrhages in the mucosa. There were no metastases.

Pancreas: This was normal.

Kidneys: There was much swelling. The right kidney was larger than the left. The capsules were free; there was some congestion of the stars of Verheyen, and the markings in the cortex were blurred. No metastatic nodules were noted.

Small intestines: These were normal. Solitary follicles of the colon were enlarged and pigmented. In the rectum, the mucosa was deeply congested. No ulcers were present.

Pelvic peritoneum: This was deeply congested, especially over the body of the uterus. Both broad ligaments were of normal thickness and the ovaries and tubes were normal in size and appearance.

Uterus: The body measured 1.25 cm. in length and was free from tumor nodules. Its lining was congested and showed a linear area of hemorrhage extending along the entire body, just to the right of the median line. The cervix was 2.25 cm. long. The outlines of both lips and of the folds of the mucosa were lost in the tumor mass, so that only 3 mm. of the anterior lip retained its outline and free border.

Vagina: This was filled and distended with a cauliflower-like mass extending over and adherent to the entire posterior wall to a point within 0.5 cm. of the outlet. The mass also involved the lower half of the cervix uteri on the right side and the lower two-thirds on the left side. The uterine body was not involved. The greater portion of the growth was greenish black, from necrosis. A small opening through the vaginal growth into the culdesac of Douglas, just to the left of the median line, gave exit to a small amount of pus present in that pouch.

Anatomic diagnosis: (1) Neoplasm of cervix uteri and vagina; (2) purulent pelvic peritonitis, localized; (3) fibrinopurulent pleurisy; (4) pulmonary abscess, and (5) subserous hemorrhages of lungs and liver were diagnosed.

Microscopic Examination.—The first specimen submitted for examination was a collection of small pieces varying from 2 to 7 mm. in diameter, which had been curetted from the mass in the vagina. The bits of tissue were red and pink, and a small amount of clotted blood was present. On microscopic examination, four distinct points were noted: 1. There were tags of tissue from which all cell structure had disappeared, leaving the general outline of an oval, sharply limited piece taking the diffuse (eosin) but not the nuclear (hemoglobin) stain. 2. There were tags of tissue similar to those described above in size, shape and outline, but densely infiltrated with polymorphonuclear leukocytes, so that it was not possible to determine the original tissue structure. 3. There were areas consisting of blood vessels filled with red cells and having a wall of endothelial cells only. These vessels varied in size. They anastomosed in all directions, making a network of capillaries, and were surrounded by a loose stroma carrying comparatively large, irregularly round and polyhedral cells, with a clear cytoplasm and a large nucleus. Some giant cells and comparatively few spindle cells were present. There were many dividing nuclei. The picture thus presented was one of angiosarcoma, which was the first diagnosis made from these scrapings. The fourth point noted in the section was a bit composed of unstriped muscle cells, markedly infiltrated with polymorphonuclear leukocytes and partly covered with stratified pavement epithelium, the whole resembling a piece of the cervix uteri. In some fields, there were large cells resembling those seen in the third portion of the scrapings, lying around small blood vessels and between the muscle cells. The growth seemed to be of the cervical mucosa, but it had begun to infiltrate the muscle wall.

At necropsy, sections from the tumor and from the cervix and vagina beyond the growth were obtained for microscopic examination. The soft, polypoid excrescences that gave the tumor its cauliflower appearance were found to present a picture similar to that shown by the curettings, but, in addition, their relation to the vaginal wall could be traced. The large round cells were numerous and lay in a vascular stroma. Such cellular masses,

with dividing nuclei, were arranged around a central stem of connective tissue, forming a finger-like process of oval or round shape. The connective tissue stem arose from, or was continuous with, the submucosa of the vagina. Some of the processes were necrotic, but some were well preserved. At the base of some processes, there were cross or long sections of younger, smaller processes composed of a vascular stroma carrying an occasional striated cell, and surrounded by the large cells characteristic of the neoplasm. The processes seemed to branch and interlace, always with masses of the large cells between them. Long cells with more or less definite striations were present, but not in large numbers, and were entirely absent in some sections. The muscle layers

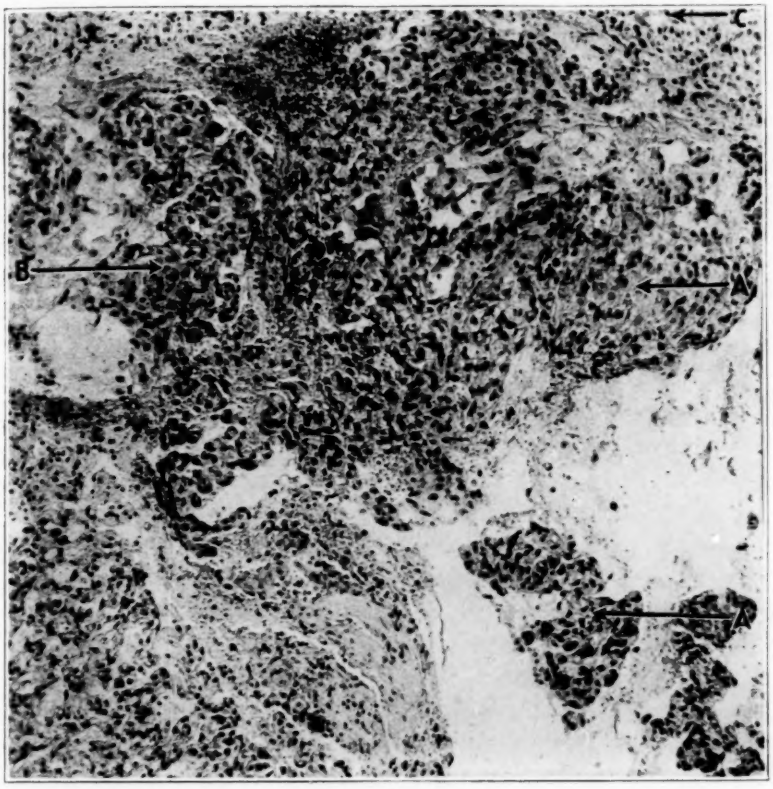

Fig. 2.—*a*, polypoid masses, with the cells, *b*, characteristic of the growth; *c*, vaginal wall. (× 130.)

of the vagina showed invasion by the tumor cells, small groups of which were present between the muscle cells, lying around and sometimes within small blood vessels.

The lowest portion of the vagina showed an unusual amount of striped muscle in its wall, the fibers varying much in size and shape.

In sections from the cervix, inflammatory infiltration and necrosis were very marked, and the tumor cells extended into the muscle layers.

Sections made from the vagina and the cervix beyond the neoplasm showed a loss of epithelium, and inflammatory infiltration of the mucosa and muscle wall.

From the scrapings obtained from the vagina when the infant was admitted to the Babies' Hospital, the diagnosis of angiosarcoma was made. The specimens taken at necropsy showed the growth to be a rhabdomyosarcoma, and thus brought it into the group of mixed tumors of the vagina, as classified by Wilms.[1]

COMMENT

There can be no doubt that the radium treatment altered the gross and microscopic picture by the destructive changes it introduced. No grapelike masses were seen, but both the scrapings and the cauliflower appearance of the growth at necropsy gave an indication of polypoid growth substantiated by the microscopic findings. In most cases reported, a mass has been noted as presenting at the vaginal orifice, or protruding from it. No such condition appeared in this child.

Pick [2] reported a spindle-cell sarcoma as the first primary sarcoma of the cervix to be recorded in a child. The symptoms began at the age of 2 years, and the child died six months later. There was a large uterine tumor present, extending as high as the umbilicus. It was so tightly adherent to the abdominal viscera and intestines that the latter were badly torn when an attempt was made to break up the adhesions. The tumor was grapelike in form, involving both the cervix and the uterus. The ovaries could not be differentiated.

Bluhm,[3] in 1903, reported the case of a polypoid mixed tumor of the cervix uteri occurring in a girl, 11 years old. She pointed out that Richter's [4] case (in a child, 2 years old), reported in 1892 as a proliferating mucous polyp, later examined by Grawitz and shown to be a mixed sarcoma, is really the first record of such a growth. We have been unable to obtain Richter's [4] original article. Bluhm's [3] patient recovered after hysterectomy. Wilms [1] accepts Ganghofner's [5] case, which occurred in a girl of 8 years, as a mixed tumor primary in the cervix uteri. Curtis [6] reported the case of an infant, 1 year old, in whom the growth originated in the anterior cervical lip and then involved the walls of the vagina, the anterior more than the posterior. The child died after operation. There is, in Curtis' case, no more proof of the cervical origin of the neoplasm than appears in our own.

Smith [7] reports a round-cell sarcoma of the uterus with mucous polypi, in a girl of 3 years and 9 months. Abdominal swelling and vaginal discharge were first noted eight months before operation. Numerous polypi protruded from the uterus. Smith [7] stated that

1. Wilms: Die Mischgeschwülste, Leipzig, 1900.
2. Pick: Arch. f. Gynäk. **46**:191, 1894.
3. Bluhm: Arch. f. Gynäk. **68**:236, 1903.
4. Richter: Cited by Bluhm (Footnote 3).
5. Ganghofner: Cited by Wilms (Footnote 1).
6. Curtis: Med. Press and Circular, New Series **76**:51, 1903.
7. Smith: Am. J. Obst. **16**:555, 1883.

several hundred of the polypi were removed through the vagina one month before the death of the patient. Wilms [1] puts this case also in the group of primary cervical sarcomas, assuming that, since the cervix was chiefly involved, the new growth originated there, as in Pick's [2] case. Nevertheless, its origin remains in doubt.

Sarcomas of the body of the uterus are exceedingly rare in children. Rosenstein [8] has reported such a case in a child not yet 2 years old.

As for mixed tumors of the vagina, they have been reported in children from 6½ months (Hauser [9]) to 7 years (Demme [10]) of age. In Demme's case, a peasized nodule was said to have presented at the vulva at birth, but did not begin to enlarge until five years later. Operation was performed at the age of 5½ years, when the growth had become as large as a peach. There were two recurrences, and the child died at the age of 7 years. Schuchardt [11] reported two cases. One of these children, 2 years old, showed a recurrence of the tumor six and one half months after operation. A second operation was performed, and the child made a complete recovery. Ten years later, she was in "blooming health," as Schuchardt wrote to Holländer [12] when the latter reported the case of a 9 months old baby who recovered after an operation for removal of a vaginal polypoid sarcoma.

The tissue elements which have been described in these mixed neoplasms of the vagina and cervix are: round and spindle cells, in practically every case reported; myxomatous tissue, wherever a polyp has been examined; unstriped muscle, rarely; striped muscle, more rarely still, and cartilage. All these elements are of mesodermal origin.

Though these tumors are malignant, they rarely metastasize to distant organs by way of the blood or lymph stream. They do extend locally, involving the bladder, parametrium and broad ligaments, and, rarely, the regional lymph nodes (Curtis [6]). They are congenital tumors, originating from cells of the mesoderm, whose embryonal potentialities are expressed in the mixed elements present in the growth. The undifferentiated cells are transported to the seat of their later development (uterus or vagina) by the Wolffian duct as it grows caudalward.

The prognosis of mixed sarcomas of the vagina and cervix in young children is bad, but not hopeless. Radical operation has resulted in cure in three cases: an 11 year old girl with a polypoid mixed sarcoma

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8. Rosenstein: Virchows Arch. f. path. Anat. **92**:191, 1883.
9. Hauser: Virchows Arch. f. path. Anat. **88**:165, 1882.
10. Demme: Cited by Pick (Footnote 2).
11. Schuchardt: Deutsch. Gesellsch. f. Gynäk., Second Congress, 1888, p. 237.
12. Holländer: Deutsch. med. Wchnschr., 1896, 22d Society Proceedings, No. 16, p. 102.

of the cervix uteri (Bluhm [3]); a 2 year old child with polypoid mixed sarcoma of the vagina (Schuchardt [11]), and an infant, 9 months old, with a polypoid mixed sarcoma of the vagina (Holländer [12]). In not one of these cases in which cure was reported were any striated muscle elements found in the tumor. Their presence is, apparently, accompanied by a greater degree of malignancy.

INDURATED ULCER OF THE TONGUE DUE TO OIDIUM LACTIS *

LAWSON WILKINS, M.D.
AND
S. BAYNE-JONES, M.D.
BALTIMORE

Oidiomycosis of the tongue, characterized by an ulcerating granuloma, is apparently a rare affection. We have not been able to find any description of cases similar to the one recently studied here, in which both the pathologic lesion of the tongue and the micro-organism concerned in its development presented unusual features.

REPORT OF CASE

History.—H. L., a male infant, had been under feeding care at the Harriet Lane Dispensary from the age of 4 months. The family history was negative. The mother had been compelled to wean the baby when he was 2 weeks old, and he had never gained weight. July 15, 1922, when first seen, he weighed 8 pounds and 14 ounces (4,025.6 gm.). His feedings were adjusted and he gained slowly until September 12, when he weighed 9 pounds and 12 ounces (4,422.5 gm.).

September 17, he became suddenly ill, with vomiting, diarrhea and fever. He passed five or six watery, greenish stools daily. September 25, the mother noticed a considerable amount of mucus and a fleck of blood in one stool. At this time, a sister, 2 years old, was suffering from a typical attack of bacillary dysentery, with characteristic bloody, mucous stools. On the basis of this, our patient's diarrhea was diagnosed dysentery, although no further blood was seen. We were unable to obtain a satisfactory mucous stool for culture. At this time, the mother first noticed a "sore" on the child's tongue.

Physical Examination.—The patient was a small, puny and emaciated infant. He was now 6 months old, and weighed 8 pounds and 15 ounces (4,054 gm.). He was pale and sallow; the skin was loose; the tissues were flabby, and there was no subcutaneous fat. The child was irritable and hypertonic, but not drowsy or dehydrated. The examination was otherwise negative except for the tongue. An ulcer was situated in the midline far back on the dorsum, about 2 cm. in front of the epiglottis. It was circular in shape, about 8 or 10 mm. in diameter, and 2 or 3 mm. deep. The edges were slightly raised and slightly undermined. The surface and overhanging edges were covered with a dirty grayish fur. The margins and base of the ulcer were hard, almost like cartilage in consistency, and felt like a button. The rest of the tongue and the mouth were entirely normal in appearance. No other ulcerations were seen, and there were no whitish flecks suggestive of thrush. The submental and the cervical lymph nodes could not be felt.

The indurated character of the ulcer was so striking that it immediately suggested a granulomatous process of some nature. The baby was tested with 0.1 mg. of old tuberculin, intradermally, and gave no reaction. A Wassermann test of the blood was negative, and a roentgenographic examination of the bones revealed no evidences of syphilis. Three weeks later, October 19, the

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* From the Department of Pediatrics and the Department of Pathology and Bacteriology, Johns Hopkins University.

Fig. 1.—Section of edge of ulcer of the tongue. The dark-staining masses are composed of the growth of Oidium in the necrotic tissue of the tongue. (Hematoxylin and eosin stain; × 100.)

Fig. 2.—Section shown in Figure 1 (× 500). The mycelial filaments of Oidium in the tissue around the ulcer of the tongue can be seen.

ulcer had not improved, and presented the same characters as before. Scrapings from the ulcer were examined under the dark field and stained with Noguchi's stain for spirochetes. No spirochetes were seen, but many yeastlike bodies and some mycelial threads were noticed. October 23, a small piece of tissue was removed from the edge of the ulcer with a curet. Sections were made and stained with hematoxylin and eosin. Cultures were also made on Sabouraud's maltose agar.

Microscopic Examination of Section.—The section from the tongue did not contain any recognizable epithelium. The tissue was composed chiefly of granular and coarsely fibrillated material which was stained diffusely with eosin and was stippled with bluish black dots of degenerated nuclei. The outer surface of the tissue was marked with a blue staining rim, and masses of this blue staining material projected downward into the red necrotic substance of the tongue (Figs. 1 and 2). The blue staining masses were composed of curved and parallel rows of granular threadlike structures with a definite contour. Septums and branches were recognizable among these mycelial filaments, especially at the thinner edges. Linear extensions of the mycelial processes penetrated the deeper portions of the tissue. There was no significant infiltration with leukocytes. No other micro-organisms, no forms of actinomyces and

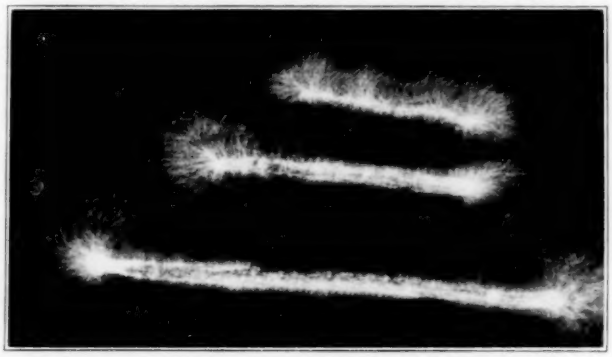

Fig. 3.—Growth of the Oidium on the surface of Sabouraud's maltose agar (natural size), showing whiteness of the growth, and filamentous edges formed by mycelia extending over the agar.

no budding forms were found in the section. The threadlike structures were undoubtedly the mycelia of a fungus.

Description of the Fungus.—The material scraped from the ulcer of the tongue was planted on Sabouraud's maltose agar, p_H 6. The organism to be described below grew readily in this medium, both at 18 C. and at 37 C. The colonies were at first flat and semitranslucent, with delicate filamentous edges. After four days, the colonies were elevated and more opaque in the center, and the edges extended in a hazy fringe of interlacing filaments. The growth was at first whitish gray, and later slightly yellowish. A stroke culture on Sabouraud's agar at the end of a week resembled a centipede (Fig. 3). The filamentous edges of the culture were at first of long straight mycelia, with few septums and with forked dichotomous branching at their ends (Fig. 4). These structures exactly correspond with the form of growth of the organism seen in the section of tissue from the tongue (Fig. 2). Later, these mycelial filaments segmented abundantly, forming rectangular cells, with rounded corners.

The morphologic changes of the organism during its growth were followed by the continuous observation of cultures in hanging drops. A round cell, or

Fig. 4.—Mycelial filaments composing the edge of a growing colony. Dichotomous branching shown at ends of mycelia. These filaments were similar to those seen in the section from the tongue; × 500.

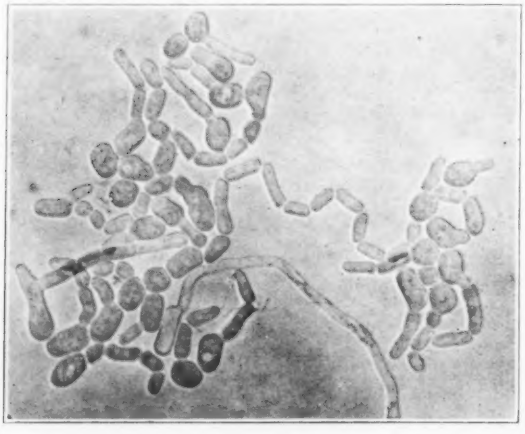

Fig. 5.—Unstained cells of Oidium in culture in a hanging drop. Large rounded forms, budding forms, rectangular cells with rounded edges and a mycelium are shown; × 1,000.

one of the elongated rectangular cells with rounded corners, extruded a bud at one corner of the cell. Some cells produced two buds. From the bud, two types of structures developed. In some cases a rapid regular sequential segmentation of the growing cells occurred, producing a chain of rounded, though almost rectangular, cells. In others, the bud grew out as a long hyaline tube, with double contour. This extended to a considerable length before segmentation occurred. Many of the mycelia branched at the extremities, forming a Y-shaped fork. Nuclear structures, vacuoles and various large and small granules were seen in the cells (Fig. 5).

The organism grew readily on ordinary culture mediums and in solutions of various carbohydrates in 1 per cent. peptone water, at p_H 7.4. A thick furry pellicle was formed on the surface of the liquid medium. The cultural reactions may be thus summarized: dextrose: acid produced without gas; lactose, sucrose, mannite and xylose: unchanged; milk: slightly acid, without coagulation; gelatin: not liquefied; Loeffler's serum: not liquefied. An identical organism was isolated from the feces.

As these morphologic and cultural characteristics are identical with those of *Oidium lactis*, this organism was compared with a type strain of *Oidium lactis* obtained from the Department of Agriculture at Washington. No difference between the two strains could be detected. On the basis of these data, the organism isolated from this patient was classified as *Oidium lactis* Link 1809. It is included in the genus *Oidium*, as emended by Pinoy to contain human parasites.

Oidium isolated from this ulcer of the tongue was not pathogenic for guinea-pigs and rabbits.

Agglutination.—The serum of the patient agglutinated a suspension of the culture of *Oidium* isolated from the ulcer of his tongue. Agglutination was definite in a dilution of 1 to 80 of the serum. The serum from several normal individuals did not agglutinate this organism.

Subsequent Course and Treatment.—Because of the loose stools, protein milk was prescribed. The diarrhea gradually responded to this treatment, and the baby began to gain in weight. December 28, the feedings were gradually changed to whole milk mixtures. Jan. 29, 1923, the child was doing well, and weighed 15 pounds and 3 ounces (6,888 gm.).

After the fungus had been identified, treatment of the ulcer was begun. October 27 to November 13, it was painted with tincture of iodin every third or fourth day. It became slightly smaller, but did not appear to be healing satisfactorily. November 13, cultures from the ulcer were again made, and the fungus was found to be present still in abundance. On the same date, the stool, which was of the claylike consistency seen with protein milk feedings, was also cultured on Sabouraud's medium. The fungus grew in great profusion on the slants. November 13, the ulcer was cauterized with a silver nitrate stick. When seen several days later, it was greatly improved. Three subsequent cauterizations, at intervals of one week, sufficed to heal it completely, leaving only a small scar.

Five weeks after the ulcer had healed completely, cultures were taken from the tongue and from the feces. No fungi grew in these.

COMMENT

A number of lesions of the mouth have been attributed to the pathogenic action of various species of *Oidium*. The most common of these affections is thrush, which has been shown to be caused by species of *Monilia* as well as varieties of *Oidium*. In thrush, there are usually multiple white flecks scattered over the mucous membranes of the mouth. The ulcerations are superficial, and the condition is often

readily cured. Castellani [1] and others have described infections of the tonsils and fauces, caused by varieties of *Monilia* and *Oidium*. In these infections, there is usually a thick dirty membrane, grayish or yellowish white, over the tonsil. Both tonsils are likely to be involved, and the membrane resembles that seen in diphtheria. We have been unable to find any report of a chronic indurated ulcer of the tongue due to *Oidium*.

There is sufficient evidence in this case to assume that the fungus isolated was the cause of the ulcer of the tongue and not merely a casual inhabitant of the mouth, or a saprophyte growing in necrotic tissue. The ulcer was chronic and indurated, and of a character not usually encountered in lesions in an infant's mouth. The microscopic section showed dense masses of mycelial threads penetrating deeply into the necrotic tissues of the tongue. No bacterial invasion was seen in the section. The fungus was agglutinated by the patient's serum and was not agglutinated by normal serum. The fungus was not found in the baby's mouth after the ulcer had healed.

The presence of the fungus in the stools is probably not of significance beyond indicating that it can be swallowed and passed through the intestinal tract without losing its viability. The association of diarrhea recalls the etiology which has been claimed for *Monilia* in sprue, but in our case there is not sufficient evidence to link the diarrhea with the presence of the *Oidium* in the stools. In all probability, the child was suffering from bacillary dysentery.

SUMMARY

In a chronic indurated ulcer occurring on an infant's tongue, the mycelial filaments of a fungus were found in great profusion in the ulcer, penetrating deep into the tissues. This fungus was isolated and identified as *Oidium lactis*. It was strongly agglutinated by the patient's serum.

The ulcer did not show much improvement after local applications of tincture of iodin, but yielded readily to cauterization with silver nitrate.

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1. Castellani, Aldo, and Chalmers, A. J.: Manual of Tropical Medicine, Ed. 3, New York, Williams Wood & Company, 1919, pp. 1093 and 1739.

SOME ASPECTS OF NEUROPATHY IN INFANCY*

CORNELIA DE LANGE, M.D.
Physician to the Emma Hospital for Sick Children
AMSTERDAM, HOLLAND

Neuropathy, by some neurologists, is said to be an acquired rather than a congenital disease. This opinion may be explained by the sphere of action of these specialists, which only very seldom permits them to study these cases in children. Otherwise, the fearful shrieks of these little ones, piercing through the closed door of the waiting room, and enabling the physician, even at a distance, to make a diagnosis with almost unfailing certainty, would long since have altered their views on this subject. A visit to the infant's ward of our hospital might serve the same purpose. We could show them the child suffering from pylorospasm and the ruminating child, the infant whose fits of restlessness and shrieking cannot be explained by bodily ailments, the baby who, after violent opposition to any variation in its diet, almost collapses from exhaustion and its fellow patient who obstinately refuses to take its feeding bottle from the hands of a strange nurse, as well the little one whose pleasure at being a center of interest makes it insensible to the pain of electric examination. Besides, we could present some patients that lie with the head bent more or less backward, without showing any symptoms of an inflammation of the ear or of an organic cerebral disease. All these peculiarities appear in infants only a few weeks, or months, old.

In these pages some observations will be made concerning three infants that presented a strong backward curve of the head.

In the second edition of Finkelstein's well known "Lehrbuch der Säuglingskrankheiten," we find an illustration of a neuropathic infant (page 191) that, besides holding its mouth open and having the small hair tuft (Freund's *Haarzopf*), is remarkable for the backward bend of the neck.

CASE 1.—Infant A, admitted to the Emma Hospital in 1915, lay in a queer attitude, which, according to the mother, it had adopted shortly after birth. The head was thrown back in such a way that the position of the face had become horizontal. The arms were folded and the legs were bent and drawn up to the abdomen. There was no question of contraction, nor did the attempts to alter the position of the infant, meet with any resistance; on the contrary, the muscles were very flaccid. As soon as the child was left to itself, it resumed its former position. It was in a state of pedatrophy. The weight, at the age of 7 months, was only 3,210 gm. The child was very pale and

* Received for publication, March 8, 1923.

restless. It ruminated, turned and shook its head, vomited frequently and continually moved its tongue forward and backward. The peristaltic waves of the stomach were slightly visible. The heart and lungs were normal, as was also the urine. There was a slight degree of tympanites of the abdomen. At times the backs of the hands and feet were somewhat edematous. The fundus oculi was normal, and the Wassermann test was negative. Besides the characteristic attitude of the patient, the most striking feature of the case was the intermittent or periodic respiration, which continued almost without interruption when the child was asleep as well as when it was awake. Figures 1 and 2 (taken by Dr. J. B. Polak) sometimes resemble the Cheyne-Stokes type of respiration and sometimes that of Biot. There never was any sign of dyspnea. The child died at the age of 10½ months.

The mother, as well as her family, had a very nervous disposition. A sister of the patient, born later, suffered from pavor nocturnus and somnambulism. To our great suprize, after obduction had been performed by Dr. Schippers, our diagnosis of "a liquid in ~~the brain~~ cerebro probably in the medulla oblongata, near the respiration center" proved to be wrong. The central nervous system and the nervi vagi were very carefully examined by Dr. Brouwer of the Central Institute for Brain Research, who did not find any abnormalities. In fact, these preparations now serve in the institute as a comparative series of a normal infant. The result of the rest of the postmortem was also negative,

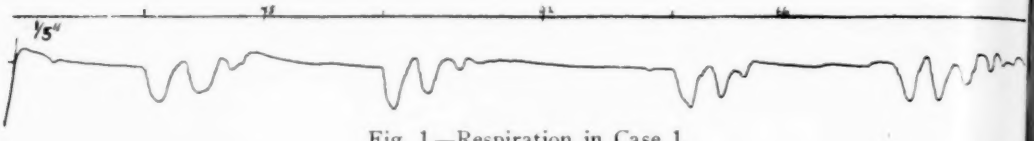

Fig. 1.—Respiration in Case 1.

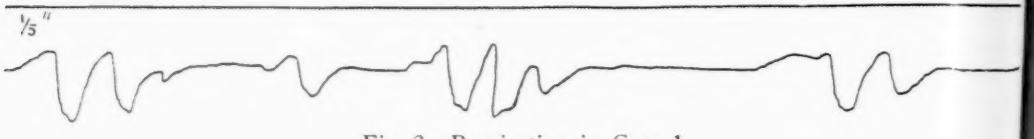

Fig. 2.—Respiration in Case 1.

except that it showed a slight fatty degeneration of the liver. We could not even find a focus of pneumonia. Thus, the child evidently died of pedatrophy.

After giving the other case histories, I will refer to this one and its characteristic respiration.

CASE 2.—Infant B, aged 6 weeks, was admitted to the Emma Hospital with a diagnosis of pedatrophy. The patient was the tenth child of the family. There had been one miscarriage; one child had died of heart disease, one of enteritis and one of a cerebral illness. The other children, as well as the father, were in good health. The mother was queer and very nervous. She stammered. The family were Mormons, of whom there are a small number in Amsterdam. The child's birth had been normal and at term. It had been bottle fed. During the previous three weeks, it lay with its head bent far backward. It was very thin and pale and weighed only 2,930 gm. The fontanel was somewhat sunken. The face and skull were slightly asymmetric. The back presented a lordotic curvature; the arms were folded, and the legs bent upward toward the abdomen (Fig. 3). Though it was possible to change this attitude without any resistance being offered, the child resumed it as soon as it was permitted to do so. The head was always bent backward, even during sleep, and it fell back as far as possible when the child was placed in a

sitting position. (In normal babies of the same age it falls forward.) The knee jerks were pronounced; the plantar reflexes were feeble and the Achilles reflex was absent.

The child had an angiospastic pallor, as is shown by the blood examination: hemoglobin (Sahli) 95 per cent.; erythrocytes 5,230,000; leukocytes 19,400; differential count: polymorphonuclear neutrophils, 33.3 per cent.; eosinophils, 0.6 per cent.; lymphocytes, 63.6 per cent.; transitionals, 1.3 per cent.; Türck's forms, 0.6 per cent. The urine was normal. The result of the electric examination of the nervus medianus was: cathodal closing, 4; anodal closing greater than 5; anodal opening greater than 5; cathodal opening greater than 5. The respiration was irregular. The patient gave a reaction to Klose's[1] suspension tests such as might be expected in a hypotonic infant. The child was hoarse and restless. It screamed a great deal, generally lay with the mouth open and ruminated. There was the little tuft described by Freund. The child did not often vomit. Still the stomach sometimes clearly presented the shape of an hour-glass. The temperature was low.

Fig. 3 (Case 2).—Appearance of child on admission.

Fig. 4 (Case 2).—Appearance of child after marked improvement.

At first but little change was noted. After a while, however, the restlessness abated. The child was often found lying in a normal position, though at intervals it resumed the former attitude, with the strongly curved back and head. The dyspepsia diminished, especially so after breast milk became available. During a stay of two months in the hospital, the increase of weight amounted to nearly 1 kg. The child laughed at times and began to look around, giving an impression totally different from that given previously (Fig. 4). The suspension tests now more or less approached the type of a hypertonic infant. It was no longer possible to make the child stroke its face with the sole of its foot. During the following months, the child developed remarkably well and appeared no different from a normal baby of the same age. Only now and then it resumed the old position.

1. Klose: Jahrb. f. Kinderh. **82**:347, 1915.

CASE 3.—Infant C, aged 3 months, was admitted to the Emma Hospital with high fever, which had lasted for some days. He was breast fed for four weeks. Afterward he was given diluted cow's milk with a small quantity of flour. Examination revealed that the left shoulder was swollen. There was an abscess on the right thigh and a small one on the back. Besides, the child suffered from otitis media. It stiffened its neck and kept it bent slightly backward. The condition improved following judicious treatment, but the child had then contracted the habit of a flaccid opisthotonus (contradictio in terminis). Even during sleep it showed a preference for a position in which the head was bent backward. No difficulty was encountered in making it

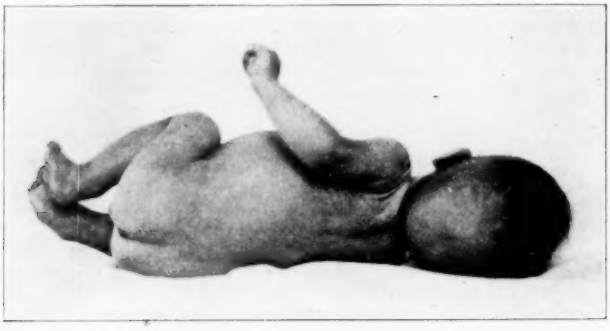

Fig. 5 (Case 3).—Appearance of infant.

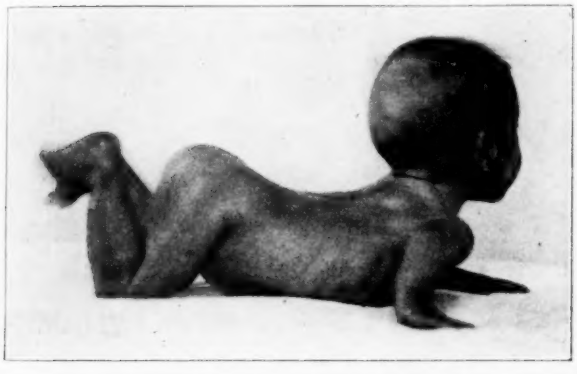

Fig. 6 (Case 3).—Appearance of infant, showing preferred position.

bend the head forward. The muscles offered no resistance, but, like the patient mentioned above, it evidently preferred the other position (Fig. 5). At times it lay in the natural attitude. The pallor of this infant also was remarkable (angiospastic pallor; hemoglobin, 87 per cent.). It vomited habitually. The mother was very nervous. The merest trifle made her cry, just as it did her mother, whose husband, the child's grandfather, was given to drink.

The baby's knee jerks were rather strong, whereas the Achilles reflexes failed. In response to the suspension test, the child behaved as does a hypotonic infant. The muscles, especially the gastrocnemii, did not feel hard. The result of the electric irritations of the nervous medianus was: cathodal closing, 3.5; anodal closing, 3.5; anodal opening, greater than 5 and cathodal

opening, greater than 5. The respiration was regular. When the abscesses were cured, the dyspepsia diminished, and the child became more lively. It assumed another attitude, although it still adhered to the backward position of the head. It lay on the abdomen with the head bent far backward and slightly turned to the left, lifting the knees from the mattress and bending the legs in such a way that the heels almost rested on the strongly raised buttocks. Generally, it kept its balance by lying on the abdomen and one forearm, but sometimes it lay on the abdomen and one knee (Fig. 6), remaining in this position for a long time, evidently preferring it. By comparing Figure 6 and and Figure 7, which represents a normal child lying on the abdomen, one is impressed by the great difference. After a while the child gave up this queer position and generally lay on his back normally. Afterward, when the dyspepsia was quite cured, the infant exhibited symptoms of exudative diathesis, eczema, strophulus and asthmatic bronchitis. At the age of 10 months, the child was dismissed from the hospital. Its mental condition was quite normal.

A few weeks afterward it was again admitted, the eczema having become worse. It no longer bent its neck backward, balancing on the abdomen, but now it delighted in throwing the head from right to left and from left to right when going to sleep and when awaking (the stereotypy, called jactatio capitis nocturna by Swoboda).

Fig. 7.—Normal child.

COMMENT

In the foregoing cases, we evidently have to do with neuropathic infants that are subject to compulsory attitudes ("Zwangslagen"). In Case 3, the attitude developed after an otitis media and an inflammation of the shoulder. In practice, we can often trace the nervous tics of older children to some slight previous ailment; for example, nervous cough may be traced to a pharyngitis; a facial tic to a corpus alienum in the eye. These three patients were not hypertonic; consequently I do not refer to Hochsinger's [2] myotonia, nor to cases of hypertonia in infants as described by Heim [3] and Klose,[1] in which opisthotonus may appear, although it very rarely does. Nevertheless, it is interesting to note that my second and third patients in their reconvalescent period

2. Hochsinger, C.: Myotonie der Neugeborenen und jungen Säuglinge, Monographie, 1900.

3. Heim, P.: Berl. klin. Wchnschr. **25**:1167, 1914.

were no longer hypotonic, but rather verged on hypertonia. This leads me to conclude with Heim that hypertonia is caused by neuropathy, whereas Klose believes that metabolic disturbances come first and bring forth the hypertonia by means of reflex. In the cases reported herewith, an excessive use of carbohydrates in the food was absent. Next to the backward position of the head, the most striking feature was the bent legs. That the arms were likewise bent is of less consequence, since the majority of young infants adopt this attitude. These neuropathic symptoms disappear along with the signs of dyspepsia, since hypersensitive infants are more easily influenced by digestive troubles and in quite a different way than are normal babies.

These infants will probably, in their future life, be afflicted by enuresis nocturna, somnambulism, pavor nocturnus, tics, nervous anorexia and phobias; in short, by any of the manifold expressions of a disturbed nervous system.

The periodical or intermittent respiration, as Hazelhoff [4] only recently remarked, cannot be satisfactorily explained by means of chemicophysiologic research and thought alone, but it requires the help of psychology. The psychic complex of respiration lies directly under the threshold of our consciousness, and, as we know, is much influenced by it. Thus, patients that exhibit the Cheyne-Stokes symptom always are in a state of strongly abated consciousness.

Secondly, it has been proved by Herzog's [5] investigations that Breuer's theory of the "Selbststeuerung der Atmung" must be applied to man as well as to animals. As Breuer learned from his experiments, every inspiration is checked and consequently shortened by stimuli, which spread through the lung vagi. Besides, the respiratory movements stop automatically on reaching a certain width, and, finally, an inspiration is caused by the diminishing of the lung volume. In man, the normal rhythm of respiration is not only regulated by the functions of the respiration center, but also by its self-government, which depend on the lung vagi and on the brain cortex. Though there is more time needed for an expiration than for an inspiration, the proportion never is 2 to 1, but generally is 1.8 to 1. Deviations from normal, accompanied by a normal gas metabolism and a normal circulation, imply an impaired autonomy. As Herzog also demonstrated from nine cases, Cheyne-Stokes respiration, besides exhibiting its well known characteristics, is peculiar because of an altered quotient E/I. At the beginning of each period, the inspiration was abnormally long, the exspiration being proportionally short; whereas, in the end, these conditions were reversed. In four of his cases, the inspiration, at the beginning of each period,

4. Hazelhoff, F. F.: Nederlandsch. Tijdschr. v. Geneesk. **2**:910 (Aug. 26) 1922.

5. Herzog, F.: Deutsch. Arch. f. klin. Med. **124,** 1918; ibid. **138,** 1921.

actually lasted longer than the expiration. In cases of cardiac failure, on the contrary, the autonomy remains unimpaired. A careful examination of the expiration curves of my patient in Case 1 (Figs. 1 and 2) shows the repeated occurrence of the inspiration, indicated by the downward curve, being absolutely longer than the expiration, indicated by the upward curve. This led me to consult the literature on respiration curves of the Cheyne-Stokes type and other types, expressing rhythmic deviations of a physiologic nature, such as may be observed during sleep and in those nervous disorders which until now have been called functional. By this study, I tried to ascertain whether the altered quotient I/E was also to be found in other curves. This proved to be the case; for example, in Mosso's [6] curve of a sleeping man, aged 77 years, in whom the Cheyne-Stokes symptom disappeared as soon as the patient began to awake; as well as in a curve of an hysterical girl, Lea, aged 18, whose case was reported by Raymond and Janet.[7] Then there are curves of irregular breathing in nervous diseases; i. e., of rhythmic deviations, which, though differing from the Cheyne-Stokes type, still repeatedly present the symptom of the inspiration being absolutely longer than the expiration. (Compare Figures 8 and 10 in Beyerman's [8] essay on "Hysteria and Respiration.") Besides, Kellog [9] relates that, in cases of insanity, he found alterations of rhythm, whereas hysterical mania repeatedly shows a lengthening of the inspiration period.

Considering that in the foregoing cases the autonomy of respiration was impaired, that the patient Lea by concentration of thought and by this only, could restore the natural rhythm,[10] and that intermittent or periodic respiration during sleep must be explained physiologically; and reflecting on Hazelhoff's remark concerning the deep sinking of consciousness which accompanies Cheyne-Stokes respiration, we are evidently justified in attributing the case of our little patient to a functional derangement of the brain cortex, the more so, since the gas metabolism and the circulation were normal and there was no trace of any organic brain disease. Here also I perceive a deep sinking of consciousness, caused by neuropathy (similar to the hysteria of Raymond and Janet), and I believe that the intermittent respiration may be explained by a periodic increase or diminution of the autonomy, as far as it is regulated by the brain cortex. Moreover, I must emphasize that infants, when

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6. Mosso: Arch. ital. de Biol. **7,** 1885.

7. Raymond and Janet sent a copy of their treatise to Dr. Beyerman, who lent it to me. The periodical in which it was published was not mentioned.

8. Beyerman: Geneesk. Bl. u. Klin. en Lab. v. d. Prakt. Series 8, No. 7.

9. Kellog: J. Nerv. & Ment. Dis., March, 1893.

10. "Thus by a totally different process Raymond and Janet came to the same conclusion which I found by experimens (namely cortical localization)" says Beyerman (Footnote 8, page 13).

awake as well as when asleep, often breathe irregularly. It looks as if the system at this age cannot function quite faultlessly. In neuropathic infants, this irregularity seems to be more pronounced than in normal ones. Hysterical hiccup repeatedly presents a ternary and a quaternary type, in which the series of shocks alternate with pauses of about equal length.[11] From Knapp's [12] investigations, we are led to seek the diaphragm center in the base of the second frontal convolution, whereas perhaps a second center may be found in the base of the precentral convolution. The field of functional nervous diseases is becoming narrowed. Perhaps the day will come when, in these cases also, an anatomic basis may be found.

The complex discussed in these pages is of rare occurrence. Besides the cases reported here, I have met it thrice in outdoor patients, who by totally overcoming the abnormal position of the head, may be said to belong to the type which I described. Therefore, we should be very careful in making this diagnosis, and should do so only in exceptional cases after long clinical observation in which special attention has been paid to the fact that there is no rigor, no opisthotonus, but that, on the contrary, the muscles are flaccid. As a rule, an infant that lies with its head bent backward is suffering from some organic disease. In such a case we should make a sad mistake if we should set the parents at ease about the state of their child.

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11. Gilles de la Tourette: Traité clinique et thérapeutique de l'hystérie **2**:182, 1895.

12. Knapp: Monatsch. f. Psychiat. u. Neurol. **50**:333, 1921; cited from Arch. f. Klin. d. heilk. **71**:316, 1922.

GASTRO-ENTEROSPASM AS A MANIFESTATION OF AUTONOMIC IMBALANCE IN EARLY INFANCY*

PARK J. WHITE, M.D.
ST. LOUIS

This paper has for its object the clearing up of certain etiologic and therapeutic misconceptions which have long been applied to the condition commonly known as pylorospasm. To date, my own observations on this subject have been entirely clinical. They have been reinforced, so to speak, by the physiologic and pharmacologic findings of others.

RELATION BETWEEN "PYLOROSPASM" AND CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

In some of our best textbooks on pediatrics, pylorospasm is considered secondarily in the discussion of congenital hypertrophic pyloric stenosis. The good results of surgery in the latter condition, and the opportunity for study of such cases on the operating table, may well be held responsible for the tendency to regard pylorospasm as a localized phenomenon, strictly confined to the pylorus, and often associated with organic hypertrophy. Such local spasm, plus increasing pyloric induration, has been advanced by many as the reason why infants with hypertrophic pyloric stenosis often do not begin to vomit until they reach the age of 1 week or more.

Now, from the mass of evidence at hand, one cannot escape the conclusion that congenital hypertrophic pyloric stenosis is a definite entity,[1] due to an underlying congenital malformation, frequently requiring surgical intervention. In a study of experimental pyloric stenosis (stenosis being produced by injection of paraffin into the walls of the pylorus), Tumpeer and Bernstein[2] state that because snakelike contraction waves are seen passing over the pyloric tumor on operation, some observers attribute the hypertrophy to this constant activity. Experimental evidence is given indicating that these contractions are caused by the tumor itself; and the important observation is made that spasm associated with the pyloric tumor of infancy is not affected by atropin.

It would be idle to dispute those who maintain that local spasm may play a part in producing the clinical picture which these cases

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* From the Department of Pediatrics, Washington University School of Medicine, and the St. Louis Children's Hospital.

1. Holt, L. E.: Hypertrophic Stenosis, J. A. M. A. **68**:1517 (May 19) 1917.
2. Tumpeer, I. H., and Bernstein, M. A.: Experimental Pyloric Stenosis, Am. J. Dis. Child. **24**:306 (Oct.) 1922.

present.[3] My object in mentioning this point is to emphasize that, as might be expected, it often causes confusion in the diagnosis of the purely functional type of expulsive vomiting, with the result that many infants have been subjected to operation who might have been cured by medical means.

Now, I have raised this question of surgical treatment early, because it is essential to the proper classification of the cases, i. e., organic and functional. It is incumbent on us, as advocates of medical treatment of infants with such motor gastro-intestinal disturbances, to explain our failures to the surgeons. After that, we may properly discuss the physiology and pharmacology of our successes. Insufficient dosage of atropin, neglect to carry out lavage or to feed thick cereal—any or all of these excellent reasons for failure of medical treatment will not justify our overlooking the fact that certain patients cannot be cured without operation. I have seen, as others have seen, patients with persistent projectile vomiting and rapid loss of weight given atropin in ample dosage, lavaged,[1] gavaged, and given thick cereal (Sauer[4]) with no resulting improvement, until operation was performed. Such cases exist because of the presence at the pylorus of a hard mass of tissue quite beyond the influence of anything except the knife. That such masses could form during the first week of life, without having begun in utero, seems inconceivable: we must concede the congenital malformation. Moreover, it is impossible to substantiate the contention that such firm, almost cartilaginous bands can be due to the activity of the vagus, even granting that this nerve supplies the pylorus.[5] The stomach and many feet of intestine are also supplied by the vagus; and why all the hyperactivity should be confined to that particular inch at the pylorus is difficult to see. Finally, when we come to consider the effect of administration of atropin, a general vagoplegic, we have an added argument against the theory of Haas that "pyloric stenosis is only an advanced degree of pylorospasm."[3] I think it safe to say that when a patient resists proper medical treatment he is suffering from that congenital malformation properly called congenital hypertrophic pyloric stenosis.

MOTOR DISTURBANCES OF FUNCTIONAL ORIGIN

If we can explain our failures on the basis of organic malformation, it is no less important to give an account of the successes of medical

3. Haas, S. V.: Congenital Hypertrophic Pyloric Stenosis and Its Treatment by Atropin, J. A. M. A. **79**:1314 (Oct. 14) 1922.

4. Sauer, L. W.: Arch. Pediat. **35**:385 (July) 1918; Pyloric Stenosis, Am. J. Dis. Child. **22**:166 (Aug.) 1921.

5. There is still some dispute about this point. Compare Salomon, A.: Monatschr. f. Kinderh. **24**:75 (Oct.) 1922.

treatment. So well do clinical observations accord with physiologic and pharmacologic studies, that therapy in these conditions may now be said to have a rational basis, as etiologic factors have more and more been brought to light.

Physiologic Considerations.—Langley [6] has classified the autonomic or involuntary nervous system thus: A. Parasympathetic: (1) tectal, (2) bulbosacral; B. Sympathetic. The enteric plexuses of Meissner and Auerbach, he classifies separately as the *enteric system,* because of the lack of proof of their central connection, and because of their very distinct histologic structure. With this system, as with that division of the parasympathetic called the *bulbar autonomic,* we are directly concerned. The bulbar autonomic supplies almost exclusively the parts developed from, or in connection with, the primitive alimentary tract: the mucous membrane of the mouth, nose and pharynx, with lachrymal and salivary glands; the esophagus, stomach, liver, pancreas, small intestine, lungs and heart, and in some animals the upper part of the large intestine. The *sacral autonomic* supplies the lower part of the large intestine, the bladder and the genitalia.

There is still some uncertainty as to the exact manner in which the nervous mechanism controlling normal gastric and intestinal peristalsis is kept in a state of balance. In the mass of work done on the subject, there is, however, nothing to discredit the theory of dual innervation. Stimulation of the parasympathetic or vagus, as is well known, will cause a definite increase in gastric and intestinal peristalsis, whether such stimulation is by electricity or by such parasympathetic drugs as pilocarpin, muscarin, arecolin, physostigmin and cholin (Langley). Stimulation of the opposing (sympathetic) mechanism, as for example by the sympathetic drug (and secretion) epinephrin, has an inhibitory effect.[7]

Bearing in mind the admonition of Alvarez [8] "not to talk with certainty about what the splanchnics and vagi will do," we may assume that the enteric plexuses are capable of maintaining normal intestinal

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6. Langley, J. N.: The Autonomic Nervous System, Cambridge, 1921.

7. Howell, W. H.: Physiology, Ed. 8, Philadelphia, W. B. Saunders Company, 1921, p. 725. How complicated a phenomenon normal peristalsis has been found to be is evident from a consideration of: Cannon, W. B.: Am. J. Physiol. **6**:251, 1902. Wheelon, Homer, and Thomas, J. E.: J. Lab. & Clin. Med. **6**:124 (Dec.) 1920; Am. J. Physiol. **59**:72 (Feb.) 1922. Wheelon, Homer: Duodenal Motility, J. A. M. A. **80**:615 (March 3) 1923. Alvarez, W. C.: Gastric Peristalsis, J. A. M. A. **79**:1281 (Oct. 14) 1922. Magnus: Arch. f. d. ges. Physiol. **102**:515, 1904; **103**:525, 1905, quoted by Sollmann, T.: Physiol. Rev. **2**:479 (Oct.) 1922. Gunn and Underhill: Quart. J. Exper. Physiol. **8**:275, 1914.

8. Alvarez, W. C., in discussion of Barber, W. H.: Enteroparesis, J. A. M. A. **79**:1825-1828 (Nov. 25) 1922.

movements, and that preponderance of vagal or of sympathetic stimuli will increase or inhibit such movements, respectively.

The sympathetic hormone, the substance maintaining normal sympathetic tonus, is epinephrin, secreted by the chromaffin system. There is now little doubt that a parasympathetic hormone exists in cholin, a less understood but most important substance whose principal action is vasodilator, with secondarily resulting fall of blood pressure. As Langley says, pilocarpin is the most familiar parasympathetic stimulant, but the action of cholin, since it is formed in the body, is more important.[9] "It is clear that if excessive production of cholin or of epinephrin occurs, it will cause a whole group of symptoms similar in the main to those caused by the parasympathetic or the sympathetic nerves."

Conversely, an insufficiency of either substance might be expected to produce symptoms referable to excessive production of its opposite. Thus, in Addison's disease, with diminished epinephrin production, we find symptoms of excessive vagus activity, including in the later stages painful vomiting, eructations, hiccup and occasional diarrhea, constipation being commoner in the earlier stages.[10]

Etiologic Considerations.—Further studies on the formation and activity of cholin may be expected to throw more light on the etiology of vagus predominance, the same factor being in all probability responsible for the clinical condition variously known as vagotonia,[11] autonomic imbalance,[12] the hypertonus of infancy[13] and *gastronévrose émétisante*,[14] not to mention the misleading term pylorospasm, which has been in common use for so long.

Functional motor disturbances of the gastro-intestinal tract, of such importance in infancy, may also be found in certain conditions of later life. Among these, we may consider the cyclic vomiting of later childhood and the hypersthenic gastric diathesis[15] of adults. Here, the gastric crises[11] of tabetics should be mentioned, due in all probability to parasympathetic involvement in neurosyphilis; also lead colic, the symptoms of which readily respond to administration of atropin.[3]

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9. An interesting study of cholin is that of Hunt, Reid: Am. J. Physiol. **45**:197-231 (Feb.) 1918.

10. Dock, George, in Osler and McCrae: Modern Medicine, Ed. 2, Philadelphia, Lea and Febiger, 1915, p. 777.

11. Eppinger, H., and Hess, E.: Nerv. & Ment. Dis., Monograph, Series No. 20, New York, 1915.

12. Lieb, C. C.; Hyman, H. T., and Kessel, L.: Exophthalmic Goiter and the Involuntary Nervous System, J. A. M. A. **79**:1099 (Sept. 30) 1922.

13. Haas, S. V.: Hypertonic Infant, Am. J. Dis. Child. **15**:323 (May) 1918.

14. Lemaire, H., and Olivier: Nourrisson **10**:305 (Sept.) 1922.

15. Hurst, A. F.: Lancet **2**:1369 (Dec. 30) 1922.

As described by Kessel, Lieb and Hyman,[16] the syndrome of autonomic imbalance, including such symptoms as tachycardia, tremor, exophthalmos, sweating, asthenia and diarrhea, may be and often is mistaken for hyperthyroidism. In the presence of normal basal metabolism, they consider that hyperthyroidism is not a factor in such cases, that the autonomic imbalance is much more likely to precede than to follow thyrotoxicosis. There is clearly no reason to implicate the thyroid as a causative factor in infantile cases.

Tetany.—According to Lemaire and Olivier,[14] contracture of smooth muscles in tetany is now an accepted fact. They report four infants with habitual vomiting, whose ages at onset ranged from 17 days to 6 months—all with clinical symptoms of pylorospasm, plus those of tetany, with no improvement until calcium chlorid was given. Certain other infants with habitual vomiting, without signs of tetany, were not helped by the calcium chlorid. Whether the vigorous motor reaction of the small intestine following the intravenous injection of sodium bicarbonate in dogs[17] is due to smooth-muscle tetany from alkalosis may still be considered open to question.[18] King and Church found that, in some cases, such reaction was diminished by administration of atropin, and in others it was not. Administration of epinephrin temporarily abolished it.

Protein Sensitization.—Since the popularization of cutaneous sensitization tests, such conditions as cyclic vomiting, the exudative diathesis and also abdominal pain alone[19] have been added to the list of conditions attributed to sensitivity to foreign protein. It is by no means unreasonable to suppose that such sensitivity can, in some cases, result in autonomic imbalance which, in severe reactions, might produce vomiting and diarrhea, such as we see in shocked dogs, associated with urticaria, etc., due to the ingestion of an offending protein. Such reaction in milder degree, however, could take the form of "peristaltic unrest." In a limited number of cases, there is unquestionably a connection between protein sensitivity, the exudative diathesis and autonomic imbalance. Two of my own cases (Cases 6 and 7) illustrate how infantile eczema and vagogenic gastro-enterospasm may exist together, and in one of these (Case 7), there was definite sensitivity to several proteins.

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16. Kessel, Leo; Lieb, C. C., and Hyman, H. T.: Exophthalmic Goiter and the Involuntary Nervous System, J. A. M. A. **79**:1213 (Oct. 7) 1922.

17. King, C. E., and Church, J. G.: Am. J. Physiol. **62**:459 (Nov.) 1922.

18. The Alleged Relation Between Alkalosis and Tetany, editorial, J. A. M. A. **79**:2232 (Dec. 30) 1922.

19. Duke, W. W.: Food Allergy as a Cause of Abdominal Pain, Arch. Int. Med. **28**:151 (Aug. 15) 1921. Shannon, W. R.: Neuropathic Manifestations as a Result of Anaphylactic Reaction to Foods Contained in Dietary, Am. J. Dis. Child. **24**:89 (July) 1922.

Parenteral Infection.—Finally, there is a further factor in the etiology of infantile gastro-enterospasm to which sufficient importance has not been attached; namely, parenteral infection. It is a matter of common experience among pediatricians that, during infancy, an acute infection, such, for example, as otitis or pyelitis, may produce vomiting and diarrhea of severity out of all proportion to the amount of infective material which directly enters the alimentary tract. Such upsets, due not to direct irritation of the alimentary mucosa, but to outside infection, should be considered vagogenic, though just how the infection so stimulates the vagus is still a matter of conjecture. Attempts to prove by skin tests that there is sensitization to the bacterial protein have been disappointing. For the present, we shall have to resort to the old generality "toxic irritation" of the vagus, as the most nearly adequate explanation.[20]

CLINICAL OBSERVATIONS

In discussing the paper by Sauer et al.[21] on gastric findings in older children with anorexia, I called attention to the fact that certain of their remarks on the relation of habitus,[22] gastric motility and appetite were applicable to motor abnormalities in infancy. I emphasized at the time that when there is pylorospasm there is also enterospasm, which hurries the food through the intestine, thus causing these infants to require more food than normal infants of the same weight and age (a mechanical rather than a metabolic hunger). Haas writes: "The chief symptoms are those of muscle spasm. . . . Colic, visible peristalsis, both gastric and intestinal, constipation,[23] vomiting, sleeplessness and constant crying make up the picture, to which is added in some cases instability of the vasomotor system as shown by cyanosis of the circumoral region, cold, clammy hands and feet, subnormal temperature and inability to make progress on any form of feeding."

Essentially the same symptoms are described by Shawkey,[24] who raises the very natural question "Why do such infants not have diarrhea?" His answer is that the anal sphincters, as shown by digital

20. Reference should be made at this point to a number of articles bearing on the subjects we have discussed: Kay, W. E.: A Study of One Hundred Cases Diagnosed as Hyperthyroidism, J. A. M. A. **79**:2149 (Dec. 23) 1922. Held, I. W., and Roemer, J.: Gastrospasm, Am. J. Med. Sc. **164**:188 (Aug.) 1922. Finney, J. M. T., and Friedenwald, J.: Pylorospasm in Adults, Am. J. M. Sc. **162**:469 (Oct.) 1921. (They found that in adults, the purely neurotic variety of pylorospasm was much less common than the irritative and reflex varieties.) Barber, W. H.: Footnote 8.

21. Sauer, L. W.; Minsk, L. D., and Alexander, W. G.: Gastric Findings in Children with Anorexia, J. A. M. A. **79**:184, (July 15) 1922.

22. Mills, R. W.: Am. J. Roentgenol. **4**:155 (April) 1917.

23. That diarrhea may occur frequently is shown by a number of the cases reported later.

24. Shawkey, A. A.: West Virginia Med. Monthly **17**:201 (Dec.) 1922.

examination, share in the hypertonicity, being so firmly contracted as to prevent the passage of stools, though these are soft when finally passed. He cites cases in which constipation has been definitely and promptly relieved by atropin, with return of the constipation when the drug was discontinued. Haas [13] also includes this type of constipation in his description of the hypertonic infant.

Now I have implied that diarrhea is rather more to be expected than constipation, emphasizing the similarity between the alimentary hyperactivity of infancy and the neurogenic diarrhea of later life. Shawkey's question as to why the infants we are discussing do not have diarrhea may be answered in part by saying that many of them do, as is illustrated by cases herewith reported. I feel sure that others will be able to report similar cases. By diarrhea, I do not mean the scanty, mucoid, frequent stools which barely stain the diaper, properly described as starvation stools. I mean true diarrhea, with copious, watery, green stools, which may appear before or after the onset of projectile vomiting (Cases 1 and 2). I do not intend to imply, however, that constipation is uncommon in enterospastic infants. Firm contraction of the anal sphincters is, nevertheless, an inadequate explanation of it. It will be remembered [25] that the parasympathetic innervation of the lower part of the large intestine is derived from the sacral autonomic. Now, autonomic drugs, such as atropin, have decidedly different effects on different divisions of the autonomic system, such effects varying with the dosage and with the individual patient or animal. Similarly, with bodily secretions: there is both pharmacologic and clinical evidence that hyperactivity of stomach and small intestine, or of the latter alone, does not necessarily involve the large intestine. Consequently, a stool may be hurried through the small intestine, to remain for a long time in the descending colon and sigmoid. In this is a plausible explanation for the green but hard stools which are not infrequently seen, the color being due to unchanged bile pigments, the firm consistency to extraction of water in the colon and sigmoid. Sphincter contraction may, of course, be an additional factor.

EFFECT OF ATROPIN ON INFANTILE GASTRO-ENTERCSPASM

Reports of results of atropin therapy vary in enthusiasm all the way from that of Haas, who considers the drug a specific, to that of Levy,[26] who does not think it necessary, largely because of his good results with thick cereal feeding. The great majority of observers—I shall not attempt a complete review—concede that administration of atropin is at least as important as lavage and thick cereal feeding. To

25. Langley, J. N.: Footnote 6. Sollmann, Torald: Physiol. Rev. **2**:479 (Oct.) 1922.

26. Levy, D. J.: J. Michigan M. Soc. **21**:166, 1922.

my mind, it is by far the most important, and usually the only essential, medical measure. It has, besides, a diagnostic value of prime importance. Often it is impossible to differentiate between organic and spastic obstruction, without resort to the therapeutic test.

Using as subjects six healthy infants from 3 weeks to 8 months of age, Salomon [5] found that atropin in a dosage of from 2 to 3 drops of a 1:1,000 solution retarded the emptying time of the stomach, food residue being found as long as five hours after feeding. After twenty-four hours of atropin therapy, he found no diminution of hydrochloric acid secretion, nor any alteration of hydrogen ion concentration.[27] Fluoroscopy revealed a relaxation of gastric tonus, dilatation of the stomach, slowing of peristalsis and increased shallowness of antral movements. No influence on the pylorus in the way of relaxation was noted,[28] which would seem to indicate that parasympathetic innervation of the pylorus may be of but little significance. The observation, however, awaits confirmation by others; and for the present, we may accept the view [2] that atropin does not exert a selective action on the pylorus, but paralyzes the vagus endings with depression of all gastric peristalsis, and, with regard to the small intestine, prevents vagus predominance, permitting the plexuses of Meissner and Auerbach to carry on normal peristalsis.

Practical Points in Administration of Atropin to Young Infants.—1. The solution should not be used when it is more than 2 weeks old.

2. A good prescription is:

		Gm. or C.c.	
℞	Atropin sulphate.....	.03	gr. ss
	Distilled water.....	30	fl ℥ i

One minim thus contains one nine hundred and sixtieth grain of atropin. It should be given in a little water, fifteen minutes before each feeding, to permit the atropin to take effect before ingestion of food. If no improvement results, the dose may be gradually increased till three or even five nine hundred and sixtieth grain is given before each of five feedings. (The four-hour interval is preferable, to allow maximum rest for the alimentary tract.)

3. The Barnes, or some other accurate minim-dropper, should be used. The solution may be placed in about half a teaspoonful of water,

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27. Contrast results of B. C. Lockwood and H. G. Chamberlin (Effect of Atropin on Gastric Function as Measured by Fractional Analysis, Arch. Int. Med. **30**:806 [Dec.] 1922, who found (in adults) that atropin in maximum clinical dosage depresses both free and total acidity 30 per cent. Their results differed further from those of Salomon in that they found bile in the gastric contents oftener after atropin therapy because of the greater pyloric relaxation.

28. Similar results were obtained by Lasch (Klin. Wchnschr. **1**:840 [April] 1922) and by Otvös (Arch. f. klin. Med. **136**:58 [April] 1921).

and given through an empty nipple. If any is lost, the mother should not try to "make it up" by giving more.

4. Unless the flushing which may follow a dose is extremely marked, no alarm need be felt. The next dose of the same amount may produce no flushing at all. However, definite flushing is evidence of sufficient dosage. Dry-mouth is not a reliable sign in early infancy.

5. Failure of pupils to react to light is one of the latest signs of atropinization; when it appears, the dose should be reduced.

6. After the baby's condition has been satisfactory for from four to six weeks, an attempt at gradual reduction of the dose should be made.

Special Indications for Feeding Thick Cereal.—Though I believe that atropin will cure all functional cases presenting, among other symptoms, those of pyloric obstruction, and that patients not thus relieved are suffering from organic stenosis, there are, nevertheless, mild degrees of the latter which, though unaffected by atropin,[2] are amenable to medical treatment. It is in such cases that thick cereal feeding is of the greatest value. Unavailing in extreme organic stenosis, unnecessary in functional gastro-enterospasm, it may often permit a child with moderate or even marked stenosis to gain or at least to hold its weight till the condition is outgrown.

It is not the object of this paper to report, from a large series of cases, the proportion responding to the different forms of treatment. With one exception, I shall present only cases illustrative of the vagogenic gastro-enterospasm which has been discussed.

REPORT OF CASES

CASE 1.—P. W., a girl, whose family history was of considerable interest, and who resembled the mother, gave a negative history on the father's side, except that "they are all high-strung." The mother's father and two sisters and the mother herself were subject to hunger-pains and unpleasant sensations if meals were long delayed. The mother's mother was free from autonomic symptoms except marked hyperhidrosis. The mother and two sisters had low blood pressure (from 90 to 100 mm. of mercury) and were very easily tired though energetic. The mother and her younger sister were subject to attacks of "unexplainable diarrhea," with abdominal cramps. There was no evidence of a high metabolic rate. The mother was subject to headaches and to hyperhidrosis.

The patient was born at term, and delivery was normal. No gain was made during the first ten days of life. There were from three to six watery stools a day during the first month, and occasionally eight or nine. The bowels usually moved after each feeding, with additional movements between feedings. She was given both breasts for a total of twenty minutes every four hours, to insure a maximum of breast milk with a minimum of bowel stimulation. At the age of 2 weeks, she began to gain from 7 to 8 ounces (198 to 226 gm.) a week. However, as she showed signs of hunger, supplementary feeding with a milk-water-and-sugar formula was begun, and eagerly taken, with neither increase nor decrease in the number of stools.

As the age of 1 month, projectile vomiting began, the diarrhea continuing. On the first day of vomiting, the baby expelled all of three feedings immediately after taking them. She screamed almost constantly; the act of feeding apparently causing great pain, and being followed by the passage of loose stools with much gas. Gastric and intestinal peristalsis were now visible. She was at once given 1/960 grain, of atropin fifteen minutes before each feeding. This was obtained from a small local drug store. No improvement resulted during the next two days. A fresh supply of atropin was bought from a more active prescription pharmacy, and after the first three doses of this preparation, the improvement in the baby's behavior was remarkable. She vomited only a few times afterward, and the number of stools was reduced from six or eight a day to two or three. While on atropin, she was more fussy than the normal baby, usually crying from 6 to 10 p. m., though taking plenty of food and gaining rapidly. The atropin, though fresh, had to be increased to 1/480 grain before feeding. Only occasional flushing resulted.

Several attempts to discontinue the atropin were made, one being followed by diarrhea so severe as to require starvation and speedy resumption of the drug. Other attempts at discontinuance were followed by extreme fretfulness, and in one instance by vomiting. Finally, at the age of 8 months, atropin was discontinued, without return of symptoms. At the age of 18 months, the appetite is still voracious, and the bowels tend much more to looseness than to constipation. The weight is normal.[29]

CASE 2.—D. D., girl, first seen at the age of 3 weeks, had had frequent stools (nine or ten daily) since birth. Nursing was painful. The baby screamed most of the time, except between 11 p. m. and 6 a. m. Projectile vomiting began at the age of 1 month. There was visible peristalsis. Vomiting occurred five times during the week. Both vomiting and diarrhea were checked promptly by atropin, 1/480 grain, given before each feeding (five feedings a day). At the age of 6 months, the patient still requires the drug. She is "fretful while taking it but frantic without it."

CASE 3.—R. G., boy, first seen at age of 4 weeks, had made no gain since birth. Projectile vomiting had occurred after each feeding, since birth. There were two constipated stools a day, green when passed. The baby was very fretful, especially when nursed. There was visible peristalsis. He was allowed to continue nursing every three hours, and was given 1/960 grain of atropin fifteen minutes before each nursing. The number of stools remained the same, but they were no longer green. The patient gained weight very rapidly and was no longer fretful. The amount of atropin was gradually decreased at age of 3 months, and administration was not resumed.

CASE 4.—A. W., girl, first seen at age of 5 weeks, was an example of the mismanagement to which such patients are often subjected, having been nursed very irregularly, treated by "any number of physicians," and given every known cathartic and other drugs in profusion. She was quite constipated, though the consistency and color of the stools were normal. She made a good recovery on atropin. As in Cases 1 and 2, this baby had to be weaned early, lack of rest for the mother being the main factor in diminishing the supply of breast milk.

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29. One cannot predict the length of time during which atropin will be required in these cases. I know of one patient who required it until the age of 15 months. It is unusual, however, to have to give it longer than from one month to three months. The fact that the condition may occur in adults has been referred to at some length. The mother of the baby in Case 1 was relieved by it, but required such large doses that great inconvenience from visual impairment resulted. The idiopathic pylorospasm of adults is probably due to autonomic imbalance, the secondary pylorospasm being due to such local condition as gallstones and appendicitis. (Compare Finney and Friedenwald: Footnote 20; also Einhorn and Scholz: Med. Rec. **98**:883 (Nov. 27) 1920.

CASE 5.—A. N., first seen at the age of 4 months, had been weaned two weeks previously and was given condensed milk. He had always "fought the breast," and was a dirty, ill-kept, athreptic baby (hospital case.) Peristaltic waves were seen, passing from left to right (a sign which may often be discounted in an athreptic baby with diarrhea). Atropin therapy, plus proper feeding, resulted in such prompt improvement that the drug was discontinued in three days and was not resumed. This was one of a considerable number of cases in which it could not be determined whether the atropin or the change to proper feeding was the principal factor in effecting cure.

CASE 6.—R. McC., boy, first seen at the age of 4 weeks, weighed at birth 6 pounds and 14 ounces, (3,118.50 gm.), and at 4 weeks, 6 pounds and 9 ounces (2,976.75 gm.). Delivery (instrumental) was difficult; and the baby was too weak to nurse. The breast pump was used in vain. The physician gave a powdered milk formula of proper strength, but whenever the baby took a sufficient quantity, diarrhea resulted, necessitating periods of starvation and administration of rice water. When first seen, the baby was passing about six greenish, watery stools a day. He was excessively fretful, with breath-holding attacks of alarming duration. The buttocks were quite "raw" from the irritating stools. There was moderate general glandular enlargement. The spleen was never palpable.

The baby improved somewhat during the first three weeks on a whole milk modification. Then a marked facial eczema appeared; the diarrhea became worse, and he was given a lactic-milk-dextrimaltose formula. He did fairly well, the number of stools decreasing to two or three a day; but the condition of the buttocks remained the same, and the gain was unsatisfactory, the weight at 10 weeks being only 7 pounds and 8 ounces (3,402 gm.). At that age, he began vomiting after each feeding, the vomiting being only moderately forceful. This condition cleared up in four days, with no change in treatment. At the age of 12 weeks, the eczema was very marked. The baby was then getting 63 calories per pound of body weight, without diarrhea or vomiting. In view of the hypothreptic condition, it was considered more important to give a high calory diet than to underfeed him, because of his eczema.

Sensitization tests for milk proteins, the only ones he was then receiving, were negative, as was also the Pirquet test. One week later, the vomiting and diarrhea returned. The weight remained stationary, and there was increasing fretfulness. At 13 weeks, the vomiting, which had been more like marked regurgitation, became projectile, entire feedings being vomited once or more often every day. After a futile attempt to check the vomiting and diarrhea by the use of skimmed lactic-acid milk, atropin was resorted to. The dose was rapidly increased (in four days) to $\frac{1}{480}$ grain before each of the five feedings given. In spite of the diarrhea at that time, the feeding was increased to whole lactic-acid milk, 24 ounces (532 c.c.); water, 3 ounces (89 c.c.); 50 per cent. corn (Karo) syrup, 3 ounces (89 c.c.). The five feedings, 6 ounces (178 c.c.) each, gave about 70 calories for each pound of body weight. The atropin was depended on to check the diarrhea. As for the diet itself, such a formula, though very concentrated, has repeatedly caused constipation in ordinary cases of infantile diarrhea, i. e. those due to fermentation and local irritation. Within four days, the vomiting had stopped; the stools were reduced to two a day; the irritated buttocks were greatly improved, and the baby seemed better in every way. Except for pneumonia and otitis at the present writing, his subsequent course has been satisfactory.

This, then, is a case combining the exudative diathesis with alimentary motor disturbance of a character more enterospastic than gastrospastic, in which administration of atropin proved practically the only efficient therapy.

CASE 7.—T. L., boy, first seen at the age of 3 weeks, the chief complaints being diarrhea, vomiting and fretfulness, was breast fed every four hours, and gained rapidly in spite of these complaints. He always had five or six green watery stools a day. The bowels always moved during or immediately after nursing, which seemed to cause great pain. A severe facial eczema appeared at the age of 6 weeks. No sensitization tests were performed, but the mother was told to stop eating eggs (Shannon). In a week, the eczema had greatly improved, only to return two weeks later, at the age of 3½ months. At this time, because of constant fretfulness, painful nursing, continued diarrhea and increasing regurgitation, atropin was started. Both the diarrhea and vomiting promptly subsided, and the baby quieted down within a week. At the age of 4 months, the eczema was so severe that sensitization tests were made. Pronounced reactions to wheat, egg white and beef serum were obtained. The mother carefully obeyed the indicated dietetic instructions; and the eczema was practically well in two weeks. The baby is now 15 months old. Atropin was discontinued after one month. The offending proteins were gradually added to the mother's dietary without return of the baby's eczema, which was most severe at onset.

Sensitization tests in a number of other cases of eczema in breast-fed babies have been disappointing, in contrast to the successful result in this case.

CASE 8.—R. W., girl, first seen at the age of 3 weeks, had suffered from projectile vomiting since the age of 3 days. There was rapid loss of weight; starvation stools, and visible gastric peristalsis. She was given an adequate course of atropin therapy without benefit. Thick cereal feeding resulted in the prompt cessation of symptoms and in rapid gain in weight.

As pointed out in the preceding discussion, this case was in all probability one of moderate organic stenosis, instead of functional gastro-enterospasm.

CONCLUSIONS

1. Congenital hypertrophic pyloric stenosis is a congenital malformation, not related to pylorospasm.

2. The term pylorospasm should be abandoned in favor of the term gastro-enterospasm.

3. Gastro-enterospasm is a manifestation of autonomic imbalance which may occur in adults as well as in children. This is not related to thyrotoxicosis, but may be due to excessive production of cholin. Tetany, protein sensitization, the exudative diathesis and parenteral infection may be associated etiologically with gastro-enterospasm.

4. The principal clinical manifestations of this condition are (*a*) great fretfulness, aggravated by feeding, perhaps with failure to gain during the first weeks of life; (*b*) projectile vomiting, with diarrhea or constipation, with or without visible gastric or intestinal peristalsis; (c) absence of tumor at the pylorus, and (*d*) ready response to atropin therapy.

5. Atropin, if sufficiently fresh, and if given in adequate dosage, is a specific for vagogenic gastro-enterospasm.